VISUAL DISTURBANCES IN NEURO-OPHTHALMOLOGICAL DISEASES WITH HEADACHE

PhD dissertation

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Introduction

Headache is a very pervasive symptom and is definitely the most common problem encountered by neurologists in their clinical practice. It affects an estimated 60-80% of the population any point in time.

The history of headache can be traced back almost to the beginning of the history of mankind. The first description of headache dates back to the third millennium BC. Headache has been written about extensively since the time of the Babylonian civilization. Migraine headache and hemicrania are also discussed in the Bible. Some very famous historical figures (e.g., Napoleon) have been known to suffer from terrible headaches. The aim of our studies was to collect data on the pathophysiology of headache.

Headache is rather frequently associated with visual symptoms, blurred vision, scotomas, phosphenes etc. The introduction of the concept on parallel processing of visual information raised the question whether in the magno- and parvocellular visual pathway were equally affected in all neurological, psychiatric or ophthalmological diseases. This study focused on the neuro-ophtalmology of headache, particularly how the whole pathomechanism effects functional or morphological alterations in the parvocellular or magnocellular visual pathways. This study attempts to provide data to the understanding the pathomechanisms of visual symptoms in cranial pain. Various theories have been suggested regarding the pathophysiology of migraine. They include the following: the neurovascular (trigeminovascular) theory, one of the oldest, states that intracranial vasoconstriction is responsible for migraine aura, and the subsequent rebound vasodilatation and activation of perivascular nociceptive nerves results in headache. Wolf & Arden (1996) based this theory on the following observations; (i) extra cranial vessels become distended and pulsatile during a migraine attack; (ii) stimulation of intra cranial vessels in an alert person induces headache; and (iii) vasoconstrictors such as ergotamine improve the headache, whereas vasodilators such as nitro-glycerine provoke an attack. In 1944, Leao proposed the theory of spreading depression to explain the mechanism of migraine with aura. This theory states that the threshold of neuronal excitability is altered, resulting in neuronal dysfunction. Patients with migraine and aura may have a state of central neuronal excitability that predisposes them to develop spontaneous depolarisation followed by suppression of neuronal function. In experimental animal studies, a noxious stimulus resulted in suppression of neuronal activity that spread slowly across the brain surface at a rate of 2-4 mm/min. The neurochemical basis of spreading depression is the release of potassium or excitatory amino acid glutamate from

neural tissue; this depolarizes adjacent tissue, which, in turn, releases more neurotransmitters, thus propagating the spreading depression. Recently, several neuroimaging studies have supported this hypothesis. Positron emission tomography (PET) scanning demonstrates that blood flow is reduced moderately during a migraine attack, but the spreading oligemia does not correspond to vascular territories. The oligemia itself is insufficient to cause impairment of function. Rather, the flow is reduced because metabolism has been reduced by the spreading depression. Sicuteri (1997) postulated that a state of dopaminergic hypersensitivity is present in patients with migraine, whereas the evidence is unconvincing (Mascia et al. (1998). Interest in this theory has been renewed recently. A variety of prodromal symptoms (e.g., yawning, irritability, nausea, vomiting) can be attributed to relative dopaminergic stimulation. Dopamine antagonists, such as prochlorperazine, completely relieve acute migraine attacks in almost 75% of cases. Another theory proposes that deficiency of magnesium in the brain triggers a chain of events, starting with platelet aggregation and glutamate release and, finally, resulting in the release of 5-HT, which is a vasoconstrictor.

The following studies were performed

1. To study scotopic visual spatial contrast sensitivity of healthy human volunteers in order to compare it to data obtained in the magnocellular (M) and parvocellular (P) neurons of macaque monkeys.
2. Acute hypoxia often results in headache. In addition, hypoxia might play a role in the pathogenesis of primary and secondary headaches. We attempted to study the effect of acute hypoxic hypoxia on the visual contrast sensitivity of healthy volunteers to see whether the visual pathways would be affected equally.
3. Migraine is one of the most characteristic causes of headache. Migraineous headache is typically associated with a series of visual symptoms. We studied the photopic and scotopic visual contrast sensitivity of migraine patients without aura to collect data on the function of parallel visual pathways.
4. Empty sella syndrome could be asymptomatic or it may be accompanied by various ophthalmological, endocrine or neurological symptoms, including headache. Because of the wide variety of visual symptoms reported in this diagnostic entity we studied ophthalmological signs of empty sella patients to see the common elements that could clarify the pathogenesis of headache.

Methods

Visual contrast sensitivity (CS)

Monocular static and dynamic CSs were measured at nine spacial frequencies (SF) (0.5, 1.2. 1.9, 2.9, 3.6, 4.8, 5.7, 7.2 and 14.3 c/deg) with a computerised test (Venus, NeuroScientific Corporation, USA). Stimuli were luminance contrast horizontal gratings with a sinusoidal luminance profile. For the dynamic test the pattern was reversed at a temporal frequency (TF) of 4, 8, and 16 Hz. The display subtended a visual angle of 13^{o} x 13^{o} and was viewed from a distance of 1 m. The background luminance was 17 cd/m^2. The maximum contrast was 70.7%. We used the following method for the measurement of contrast thresholds. First, the contrast was set at 15 dB above the mean normal value. The participants were all able to detect this submaximal contrast level. The contrast level was then decreased by 3 dB every 5 s until the subjects detected the stimulus (descending method). Then, contrast was set at 15 dB below the threshold measured with the descending method. For the ascending method, the contrast was increased by 3 dB every 5 s until subjects detected the stimulus. The whole procedure was repeated five times to obtain a mean contrast threshold at a given SF. The CS was defined as the reciprocal of the contrast threshold (Robson et al. 1966, Campbell et al. 1983). The sequences of the descending and ascending methods, the SFs tested and the static versus dynamic tests were counterbalanced across the subjects. In previous studies including clinical populations and normal control subjects, data obtained with this quick method were highly comparable to VCS values obtained with a more prolonged two-alternative forced choice staircase method (Kéri et al. 1999).

Statistical evaluation was carried out by means of ANOVA and post-hoc analysis with the STATISTICA program.

Visual evoked potentials (VEPs)

Venus visual stimulator was used to control the contrast and spatial frequency of the stimulus patterns. Sinusoidal gratings were generated on a computer monitor. Six spatial frequencies, ranging from 0.5 to 8.0 c/deg, were then presented in a random order to each subject. The stimulus rate was 4.0 Hz (reversals/s). The mean luminance of the TV monitor was 9 cd/m^2. The mean luminance was changed with the help of a set of neutral density filters with decreasing transparency. The actual luminance was calculated by taking into account the

luminance of the monitor and the transparency of the filter. The area of the display was rectangular and subtended a visual angle of 10.6^{o} x 6.9^{o} of at a viewing distance of 100 cm. Subjects were seated comfortably and were asked to keep their eyes on the central fixation point.

For recordings, silver-silver chloride electrodes were applied to the scalp with collodion. The electrode impedance was kept below 5 kΩ. The VEP was recorded from a mid-occipital electrode (2.5 above the inion) against a reference electrode placed on the linked earlobes. Grounding was out on the forehead. Electrical signals were amplified in a bandwidth of 0.5-100 Hz. The biological signals were analysed by a Venus signal processor system. The analog data were digitized at a sampling rate of 1000 Hz and 75 samples of 1 s epochs were averaged. The averaged response was then subjected to fast Fourier transforms, which yielded the amplitude and the phase lag of the second harmonic response to the stimulation.

In order to investigate the scotopic and photopic visual functions, the CS and VEP procedures were repeated at three luminance levels: 9, 0.9 and 0.09 cd/m^2. Decreasing of the mean luminance was achieved by using neutral density filters with decreasing transparency. There was an adaptation interval of 20 minutes to each luminance level.

Study 1.

Human scotopic contrast sensitivity: A comparison of psychophysical and electrophysiological data

Abstract

Static and dynamic contrast sensitivities (CSs) and steady-state visual evoked potentials (VEPs) were measured in photopic and scotopic conditions in 18 healthy volunteers. Results from the CS experiment indicated that the inclusion of temporal modulation and the application of scotopic luminance levels uniformly resulted in a relative increased sensitivity for low spatial frequencies. Similarly, the analysis of the second harmonic component of VEPs demonstrated a shift from band-pass to low-pass functions. These results indicate that in scotopic conditions, human visuo-spatial processing is characteristically predominated by the functional activity of magnocellular pathways.

Introduction

The existence of separate visual pathways in the primate brain has been proved by both anatomical and physiological methods (for reviews see Lennie 1980 and Shapley 1990). The importance of the parallel visual pathways has been accentuated by reports that certain human pathological processes damage selectively either the magnocellular or the parvocellular pathway (Bassi & Lehmkuhle 1990; Barnard et al. 1998; Demb et al. 1998; Steinman et al. 1998; Vogt et al. 1998; Vidyasagar & Pammer 1999). Several attempts have been made to clarify the human magnocellular functions. Various techniques and mathematical procedures have been used to assess the relative contributions from the underlying neural mechanisms (Conte et al. 1983; Thompson & Drasdo 1992; Baseler et al. 1995; Klistorner et al. 1997; Valberg & Rudvin 1997). Similarly, specific stimulation techniques have been introduced. Thus, apparent movement stimulation and motion onset stimulation have been employed in some physiological and clinical studies (Kubova et al. 1995; Tobimatsu et al. 1995). Likewise, light flickering at high frequency and low-contrast has been repeatedly used to distinguish between magnocellular and parvocellular functions (Regan et al. 1973, 1989, Nakayama & Mackeben 1982; Kulikowski et al. 1991, Fiorentini et

al. 1991, Regan & Lee 1993; Klistorner et al. 1997). Nonetheless, it seems that a sensitive and elective method for the detection of magnocellular function and damage is still not available.

The parallel processing of visual signals under photopic and scotopic conditions was suggested in the duplicity theory of Schultze (1866). Further anatomical evidence is available that the parvocellular pathway contributes weakly to night vision in primates (Hassler 1966). Recent physiological data revealed the characteristic contrast gain and temporal integration signatures of the magnocellular and the parvocellular pathways. In 1986 Purpura et al. reported that low-contrast spatial frequency (SF) light stimuli at scotopic luminance levels stimulate exclusively magnocellular ganglion cells in the monkey retina. In other laboratories this finding has been either verified or disputed (Kremers et al. 1992; Lee et al. 1993). In spite of the extensive laboratory research, scotopic stimulation has not been introduced into studies of human magnocellular pathologies. There are two major caveats that generally discourage investigators from the application of scotopic visual sensitivity in the study of magnocellular functions. First, the convergence of rod and cone signals on both parvocellular and magnocellular ganglion cells have been repeatedly reported (Enroth-Cugell et al. 1977, Gouras & Link 1966). Second, Lennie & Fairchild (1994) found that scotopic acuity over a range of eccentricities is much better than can be predicted by the distribution mosaic of magnocellular cells there. In contrast, Drum et al. (1986) and Glovinsky et al. (1992) described a decreased scotopic sensitivity in patients suffering from glaucoma, which is considered to be a disease that might exert a selective damage on the magnocellular neurons.

In the present study we have investigated human photopic and scotopic contrast sensitivity (CS) functions in healthy volunteers with good sight. We employed two methods to approach this question. First, the introduction of computer-based measurements of CSs afforded a possibility of investigating scotopic contrast sensitivity automatically and reliably under both static and dynamic conditions. Further, steady state visual evoked potentials (VEPs) were elicited by rapid repetitive stimulation. The second harmonic component of these steady-state VEPs is regarded as a hallmark of visual function (Regan 1989; Bodis-Wollner et al. 1986). They might serve as a tool for the objective measurement of human spatial frequency sensitivity. Steady-state VEPs have never been recorded under scotopic conditions, although scotopic transient pattern-reversal VEPs has recently been described (Benedek et al. 1993). The results obtained by means of the psychophysical and electrophysiological methods can be used for a comparison with physiological data obtained in single-unit recording experiments.

Subjects

Eighteen healthy adults (10 males and 8 females) ranging in age from 18 to 30 years served as subjects for the VEP study. Ten subjects (6 males and 4 females) participated in the CS experiment. All had a corrected Snellen visual acuity of 1.0 or better.

Results

Visual contrast sensitivity

Raw data were $\log_{10}$ transformed. A 3 (luminance level) x 4 (TF) x 9 (SF) ANOVA was conducted on the log-transformed CS data. Type II errors were controlled with the Greenhause-Geisser correction. There were significant main effects of luminance level ($F(2,27)=491.35$, $p<0.0001$), TF ($F(2,61)=237.69$, $p<0.0001$), and SF ($F(2,64)=822.80$, $p<0.0001$). All the two-way interactions were significant ($F>9$, $p<0.0001$). In addition, we obtained a luminance level by TF by SF interaction ($F(48, 648)=6.16$, $p<0.0001$).

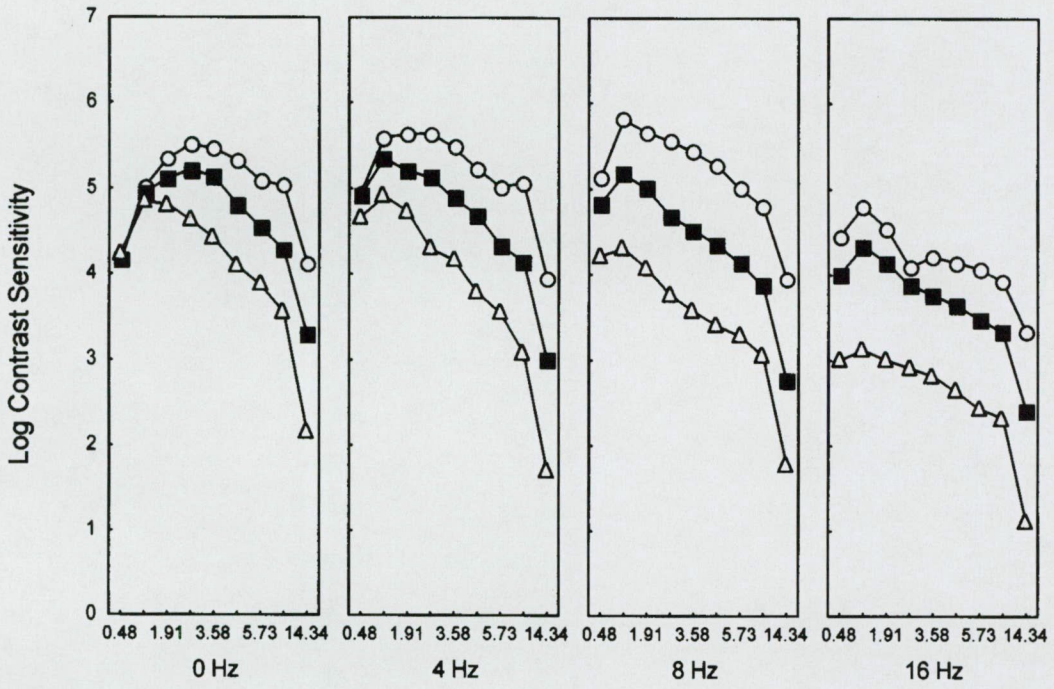

Fig. 1. Photopic and scotopic contrast sensitivity functions of healthy human subjects. The figure shows mean sensitivity values at 9 spatial and 4 temporal frequencies set at 3 luminance levels. SF – spatial frequency, circles - 9 cd/m^2, filled squares - 0.9 cd/m^2, triangles - 0.09 cd/m^2. Different temporal frequencies are presented in separate graphs. The ordinates of the graphs relate to spatial frequencies in c/deg.

As Fig 1 shows, under static and photopic conditions the contrast sensitivity revealed band-pass characteristics. Decrease of the overall luminance to the scotopic level shifted the peak values to lower spatial frequencies with a peak at around 1.2 c/deg. Increase of the TF similarly abolished the band-pass character of the photopic function. At SFs of 8 Hz and above, all curves showed the same relative preference to low SFs as under static scotopic conditions.

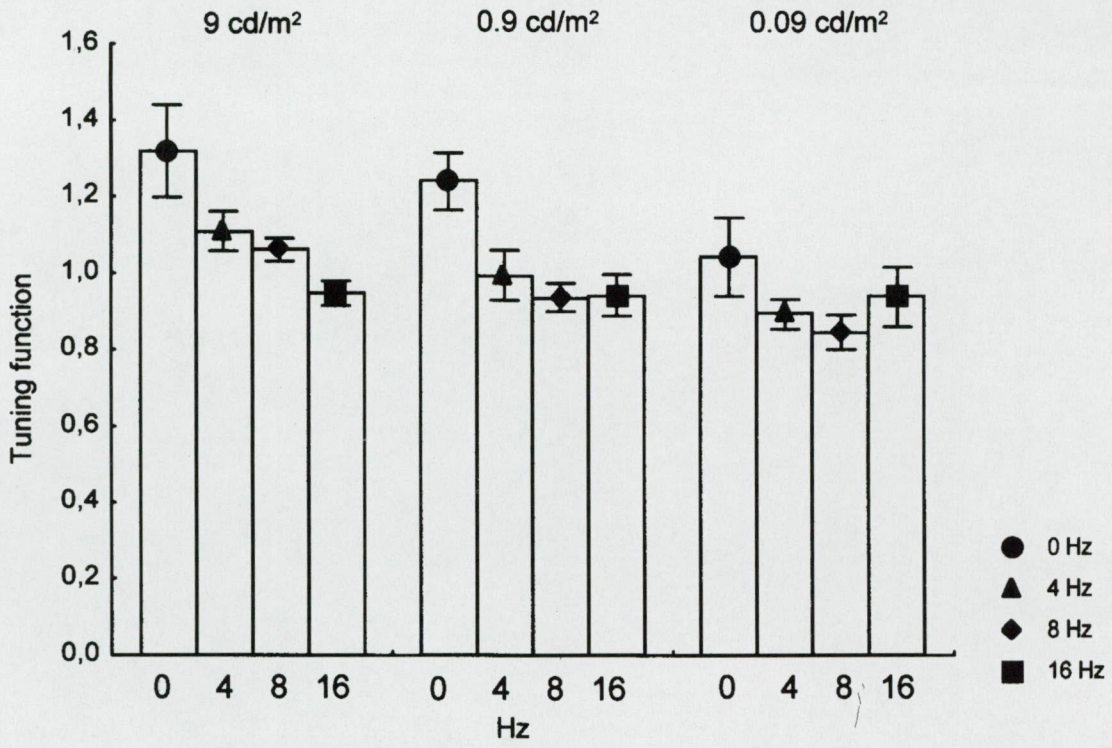

Fig. 2. Tuning functions at 4 temporal frequencies and 3 luminance levels. Tuning functions were calculated as the ratios of contrast sensitivities measured at 2.9 c/deg and 0.5 c/deg. Abscissa: temporal frequencies as shown by symbols.

Tuning functions were defined as ratios of log CCs measured at 2.9 and 0.5 c/deg. A luminance level by TF ANOVA indicated main effects of the luminance level ($F(2,27)=44.54$, $p<0.0001$) and TF ($F(3,81)=123.73$, $p<0.0001$). The two-way interaction was also significant ($F(6,81)=10.73$, $p<0.0001$). Tukey's HSD tests demonstrated significant differences between the tuning functions determined at the three luminance levels ($p<0.05$), with the exception of the highest TF (16 Hz) (Fig. 2).

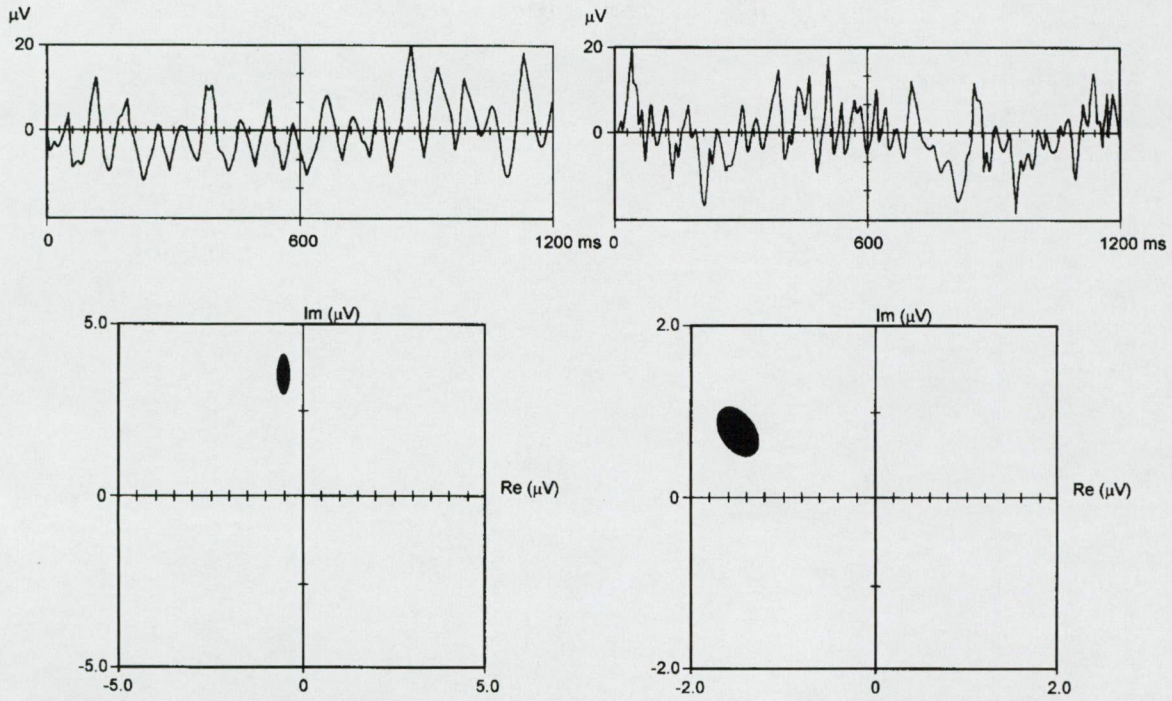

Fig. 3. Top: steady-state visual evoked potentials in response to a temporal frequency of 1/s at a spatial frequency of 1 c/deg under photopic (left) and scotopic (right) circumstances. Abscissa: time, in ms. Ordinate: voltage, in μV. Bottom: Fourier spectra of steady-state visual evoked potentials recorded under photopic (left) and scotopic (right) circumstances. Shadowed areas indicate variances. Im and Re indicate the imaginary and real axis, respectively, in μV.

Steady-state VEP

A luminance level by SF ANOVA conducted on the VEP amplitudes indicated significant main effects of the luminance level ($F(1,18)=27.36$, $p<0.001$) and SF ($F(5,90)=25.47$, $p<0.0001$). The two-way interaction was significant ($F(5,90)=13.63$, $p<0.0001$). The post hoc tests (Tukey's HSD) demonstrated reduced amplitudes in the scotopic condition ($p<0.05$). Within-condition comparisons revealed that the amplitude measured at the lowest SF in the scotopic condition was higher than the scotopic amplitudes for higher SFs ($p<0.05$) (Fig. 3, 4). The amplitude value at the lowest SF was also significantly higher than the predetermined noise level ($p<0.01$).

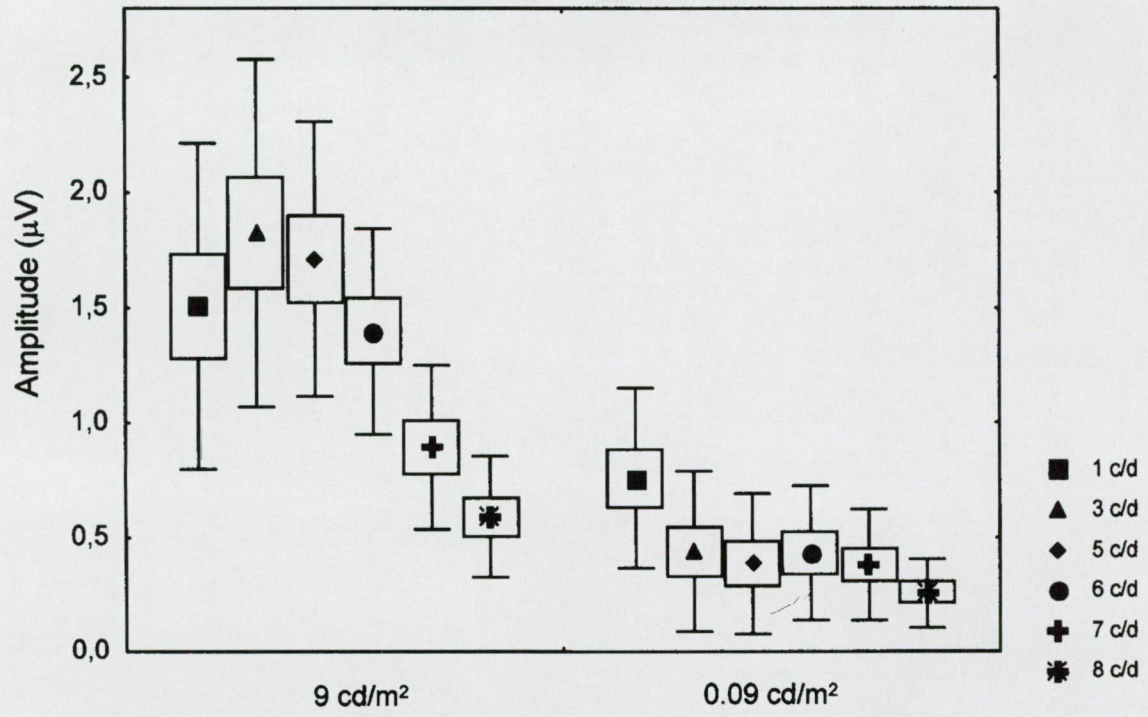

Fig. 4. Mean amplitudes (µV) of the steady-state visual evoked potentials as a function of spatial frequency in the 18 experimental subjects. The amplitude of the second harmonic responses of the Fourier spectra obtained in each recording was used in calculating the statistical values. Error bars indicate standard deviations, and boxes indicate standard errors. Abscissa: spatial frequencies as shown by symbols.

Discussion

In the experiments described above, both the psychophysical CS functions and the Fourier transformation values of the steady-state VEPs revealed characteristic differences between the photopic and scotopic visual functions. The effect of decreasing luminance on the CS curves measured for sinusoidal gratings was twofold. First, the CS decreased as the luminance was decreased. Second, the shape changed from a band-pass to a low-pass characteristic. These observations conform well to the results published in the literature (Patel 1966; Daitch & Green 1969; Kulikowski 1971; Van Meeteren & Vos 1972; Kelly 1972; Koenderink et al. 1978, Hofmann et al. 1990; Derefeldt et al. 1979; Lundt et al. 1983). However, none of the above studies stressed that the photopic and scotopic CS functions overlap almost perfectly with the CS functions measured in the parvocellular and magnocellular ganglion cells. Magnocellular ganglion cells in the retina (Lennie & Fairchild 1994), and in the dorsal lateral geniculate nucleus (Hicks et al. 1983), and cells in layer 4C

(Hawken & Parker 1984) display a similar contrast sensitivity function to that observed in humans under scotopic circumstances.

The second line of evidence for the dominant participation of the magnocellular pathway in scotopic vision comes from a comparison of the dynamic CS functions under photopic circumstances with the scotopic static CS functions. There was a relative elevation of low spatial frequency CS values at higher TFs measured under photopic conditions. These photopic dynamic CS functions were highly similar to the characteristic scotopic low-pass CS values recorded under both static and dynamic conditions. For example, separate post hoc comparisons demonstrated no significant differences between photopic CS functions at 8 Hz and scotopic static CS values. The strong correlation between the photopic dynamic and scotopic static CS functions suggests that the same neural substrate underlies both functions. Previous studies have demonstrated that the magnocellular pathway and its cortical projection sites are sensitive to low SF and high TF stimuli (for reviews see Bassi & Lehmkuhle 1990; Merigan & Maunsell 1993). Thus, the relative elevation of low SF values at higher TFs may reflect magnocellular functions. The superiority of dynamic CS in the low SF range was earlier confirmed by Lundt et al. (1983) and Ginsburg et al. (1984). Long & May (1992) suggested first that low SF channels might play an important role in dynamic visual functions, although they could not put forward much evidence in support of this suggestion.

The third set of evidence for the dominant role of magnocellular activity in scotopic visual functions has been provided by the results of our electrophysiological experiments. The second harmonics of the Fourier transforms showed the band-pass and low-pass filter characteristics for the photopic and scotopic stimulating circumstances, respectively. Both the shapes of the functions and the SF maximum revealed similar characteristics in the psychophysiological and electrophysiological experiments. Although Fourier transformations of photopic steady-state VEPs have been studied repeatedly earlier, no study has been published on the Fourier transform of steady-state VEPs under scotopic conditions. Thus, the low-pass characteristics of the scotopic steady-state VEPs have not been revealed. The question still arises of whether the low-pass characteristics can be a consequence of a floor effect, as only the lowest SF stimulation caused significant 'driving' under scotopic conditions. However, the significant SF interaction with luminance effects in the ANOVA test warrants the physiological significance of the data.

In summary, our experiments have provided psychophysical and electrophysiological evidence for the dominant role of magnocellular pathways in scotopic visual activity in humans. Our findings, together with those from single-unit animal experiments, justify the

introduction of scotopic tests into experimental or clinical studies with the aim of the estimation of magnocellular functions. The possible minor contribution of parvocellular cells in rod-mediated scotopic mechanisms (Kremers et al. 1993, Grünert 1997) should be borne in mind, although the parvocellular rod input under scotopic conditions seems rather small and might be neglected under clinical conditions. Similarly, the time-consuming dark-adaptation process might contradict the general use of the process. Nevertheless, this type of investigation indicates at least some preliminary clinical trials.

Study 2.

Hypobaric hypoxia improves visual contrast sensitivity

Abstract

The effect of hypoxia on early visual functions remains a controversial area of research. To explore this question, we measured static and dynamic visual contrast sensitivity (VCS) in 14 healthy volunteers at a simulated altitude of 5500 meter. In comparison with the baseline condition (mean arterial oxygen saturation (AOS): 98.4%), VCS significantly increased after 5, 10, and 15 min of hypoxic exposure (AOS: 82,9%, 77.0%, 74.3%, respectively). After 10 min, this improvement was markedly pronounced under dynamic conditions. Returning to the baseline altitude (AOS: 97.7%), the VCS values showed recovery mostly in the lower spatial frequencies. There was a significant negative relationship between the AOS and the VCS values at low- and medium spatial frequencies (0.5-4.8 c/deg). These results suggest that there are some perceptual or cognitive functions that show improvement during acute hypoxic challenge.

Introduction

The availability of adequate amount of oxygen is a substantial condition for the proper functioning of the nervous system. It is well established that cerebral anoxia may cause severe and irreversible neuropsychological and neuropathological impairments, affecting memory, visuospatial functions, and personality (Caine et al. 2000). Hypoxia also induces early and reversible dysfunction in mental performance. Most of the related studies revealed deficits in higher cognitive operations, including attention, executive functions, and memory (Nelson et al. 1990, Regard et al. 1991, Bartholomew et al. 1999). However, results show a definitive degree of controversy, which is particularly prominent regarding the question of early visual functions. While initial reports showed increased luminance thresholds in target detection tasks (Kobrick et al. 1983), later studies have failed to demonstrate visual contrast sensitivity (VCS) impairments (Kobrick et al. 1988, Davis et al. 1995). It is generally concluded that early (preattentive) visual functions are less altered by hypoxia, while attentive processes are markedly disrupted (Stivalet et al. 2000). In contrary, Flower et al. (1997) proposed that prolonged reaction times from visual detection tasks are based on the impairment of early visual information processing. Finally, Schlaepfer et al. (1992) found improved reading speed during a rapid and mild hypoxic challenge, which suggests that exposure to hypoxia, does not

invariably impair mental performance. To gain more insight into this important and controversial area of research, we measured static and dynamic VCS at a simulated altitude of 5500 meter. This altitude provided a marked hypobaric hypoxia, which induced impaired attentional - executive processes in a previous experiment including a visual discrimination task (Czigler et al. 1999).

Materials and methods

Subjects

Fourteen healthy male subjects with normal or corrected-to-normal visual acuity participated in the study (mean age: 32 years). All volunteers gave their written informed consent. The experimental protocol has been consented by the Ethical Committee of the Albert Szent-Györgyi Medical Center, University of Szeged.

General arrangement of the experiment

The experiment included the following steps: (1) practice trials (data not included in the analysis); (2) measurement of baseline VCS in each participant (first control); (2) measurement of VCS after 5, 10, and 15 min hypoxia exposure in a hypobaric chamber (5500 m, 0.5 atm, 21 °C); (3) measurement of VCS immediately after the normalisation of oxygen pressure (second control). In this way, we employed 2 normal (control) and 3 hypobaric hypoxic conditions. Arterial blood oxygen saturation, blood pressure, heart rate and ECG were closely monitored and registered, and a skilled physician was present in the chamber during the experiment. The contact between the participant and the experimenter was maintained with an audiovisual system. The display was located outside the chamber.

Results

The participants tolerated well the hypobaric hypoxic condition and reported no subjective feeling of visual problems. In this condition, however, we observed a marked alteration in VCS functions. First, raw data were $\log_e$ transformed and were entered into a 5 (condition) by 2 (TF) by 9 (SF) analysis of variance (ANOVA). There were main effects of condition ($F(4,63)=12.30$, $p<0.0001$), TF ($F(1,63)=5.05$, $p<0.05$), and SF ($F(8,504)=369.09$, $p<0.0001$). The condition by SF and the TF by SF interactions were also significant ($F(32,504)=1.96$,

$p<0.002$ and $F(8,504)=68.42$, $p<0.0001$, respectively). All other interactions remained below the level of statistical significance ($p>0.1$) (Fig. 1).

To explore the origin of the condition by SF interaction, 3 separate ANOVAs were conducted. First, the above-described 3-way ANOVA was used with 4 conditions (the first control and the 3 hypoxic conditions). This ANOVA indicated main effects of group ($F(3,50)=14.82$, $p<0.0001$), TF ($F(1,50)=4.65$, $p<0.05$), and SF ($F(8,400)=292.69$, $p<0.0001$). While the TF by SF interaction was significant ($F(8,400)=49.44$, $p<0.0001$), the condition by SF interaction was not ($p=0.98$). When the two control conditions were compared with the 3-way ANOVA, there was again a main effect of condition ($F(1,26)=9.08$, $p<0.01$), and the condition by SF interaction was also significant ($F(8,208)=3.61$, $p<0.001$). Post hoc t-tests indicated that the difference between the two control conditions was the largest at the highest SFs (static: 7.2 c/deg: $t(26)=-2.05$, $p=0.05$; 14.3 c/deg: $t(26)=-2.06$, $p<0.05$; dynamic: 14.3 c/deg: $t(26)=-3.50$, $p<0.002$, all other SFs: $p>0.1$) (Fig. 1). Finally, when the hypoxic conditions were compared with the second control, there was a main effect of condition ($F(3,50)=3.91$, $p<0.02$). Again, the condition by SF interaction was significant ($F(24,400)=2.31$, $p<0.001$). In addition, the condition by TF interaction also reached the level of statistical significance ($F(3,50)=2.83$, $p<0.05$). When static and dynamic VCS values were averaged across the SF and were compared with t-tests, the dynamic values exceeded the static values in one and only condition: after 10 min of hypoxic exposure ($t(12)=-3.16$, $p<0.01$; in all other conditions $p>0.1$) (Fig. 2).

Spearman's correlation coefficients (R) were calculated between the arterial blood oxygen saturation and the VCS values. In both static and dynamic conditions, there were significant negative correlations at low and medium spatial frequencies (Table 1).

Discussion

We found significantly increased VCS values in a hypobaric hypoxic condition achieved by a simulated altitude of 5500 meter. This finding contradicts to earlier reports (Kobrick et al. 1983, Kobrick et al. 1988, Davis et al. 1995), and supports the view that not all perceptual and cognitive functions are impaired during short hypoxic challenge. Potentially, at least three specific factors may contribute to this controversy: the degree of altitude, duration of hypoxic challenge, and stimulus luminance. For example, Davis et al. (1995) found degraded visual acuity after 30 min of 4300 meter, but VCS remained unaltered during the whole testing procedure. Kobrick et al. (1998) used a very high altitude (25000 feet) in a gradually

ascending manner and again found no CS alterations. In contrary, we observed a marked increase even after 5 min of hypoxic exposure, which was sustained during the whole 15 min of experiment and promptly returned near to the baseline level after the normalization of oxygen pressure, with the exception of highest SFs. It is also possible that different luminance levels contributed to the heterogeneity of results, since higher luminance levels are less likely to be affected by hypoxia (Kobrick et al. 1988). Nevertheless, increased VCS function in hypoxic conditions has never been documented before.

Although VCS is fundamentally considered as an index of early visual processing (mainly including retinal factors) (Campbell et al. 1983), it cannot be excluded that attention factors contributed to our findings. However, it is generally reported that vigilance is impaired or unaltered in hypoxic conditions (Bartholomew et al. 1999), which can hardly explain increased VCS. In a previous visual discrimination task performed in the same chamber with the same experimental design, subjects showed significantly impaired attention functions (Czigler et al. 1999). Further studies are warranted to clarify the potential contribution of attention to altered visual sensitivity under hypoxic conditions.

The physiological effects of hypoxia on the visual system are poorly understood despite its significance in clinical research and in applied sciences such as aviation and space medicine. Electrophysiological experiments investigating the cat retina revealed a marked resistance to decreased oxygen availability (Linsenmeier et al. 1990). In general the outer retina is more sensitive to hypoxia, because of the high oxygen consumption of photoreceptors and the poor vascular regulation therein. Retinal hypoxia has significantly contribution to various clinical states such as diabetic retinopathy. Harris et al. (1996) found that hyperoxia improved VCS in patients with early diabetic retinopathy, while such effect were not observed in normal controls. It can be that mild and transient hypoxia increases retinal sensitivity, whereas chronic prolonged states with irreversible tissue alteration lead to visual loss. Recent reports suggested that abnormal oxygen supply of the outer retina might play a role in the development of photoreceptor dystrophies (Stone et al. 1999). It is of particular interest that hypoxia may be a protective factor in some circumstances (Bowers et al. 2001). Schmeisser et al. (1997) found that prolonged heavy exercise at higher altitudes (4200 m) was accompanied with a decrease in visual acuity; while at moderate altitudes (2200 m) there was a decrease in electroretinographic photopic flicker responses indicating a shift in retinal cone physiology. The method of the present study allowed us to measure VCS at multiple static and temporally modulated SFs. It is of particular interest that the level of arterial oxygen saturation correlated inversely only with the VCS values obtained at low and

medium SFs, but not at high SFs. This effect is not due to the restricted variance of VCS data at higher SFs (Table 1). In general, the hypoxic challenge did not increase VCS in a strong SF- or TF-specific manner. However, when the hypoxic conditions and the second control were compared, there was a more pronounced elevation for dynamic values after 10 min of hypoxic exposure, which appeared as a condition by TF interaction (Fig. 2). This finding, together with the selective correlation data and the lack of rapid normalisation at high SFs, raises the possibility that visual subsystems with characteristic spatial and temporal properties (i.e. the magno- and parvocellular channels) may be differentially affected by hypoxia (Lennie 1980, Bassi & Lehmkuhle 1990).

Conclusions

Hypobaric hypoxia markedly improves static and dynamic VCS. The degree of improvement at low and medium SFs (0.5-4.8 c/deg) inversely correlates with the arterial blood oxygen saturation. The relationship of the VCS improvement with attention alterations and visual magno- and parvocellular functions warrants further investigation because of its potential clinical importance.

Table 1. Correlation between contrast sensitivity and arterial blood oxygen saturation

SF	R static	p static	R dynamic	p dynamic	SD static	SD dynamic
0.5	-0.61	<0.0001	-0.44	<0.0002	0.93	0.42
1.2	-0.60	<0.0001	-0.61	<0.0001	0.83	0.37
1.9	-0.58	<0.0001	-0.55	<0.0001	0.74	0.41
2.9	-0.51	<0.0001	-0.59	<0.0001	0.68	0.45
3.6	-0.41	<0.0005	-0.50	<0.0001	0.67	0.48
4.8	-0.30	<0.02	-0.43	<0.0005	0.62	0.50
5.7	-0.19	>0.1	-0.10	>0.1	0.59	0.51
7.2	-0.10	>0.1	-0.13	>0.1	0.68	0.61
14.3	-0.11	>0.1	-0.14	>0.1	0.89	0.91

SF – spatial frequency (c/deg), R - Spearman's correlation coefficient, SD – standard deviation

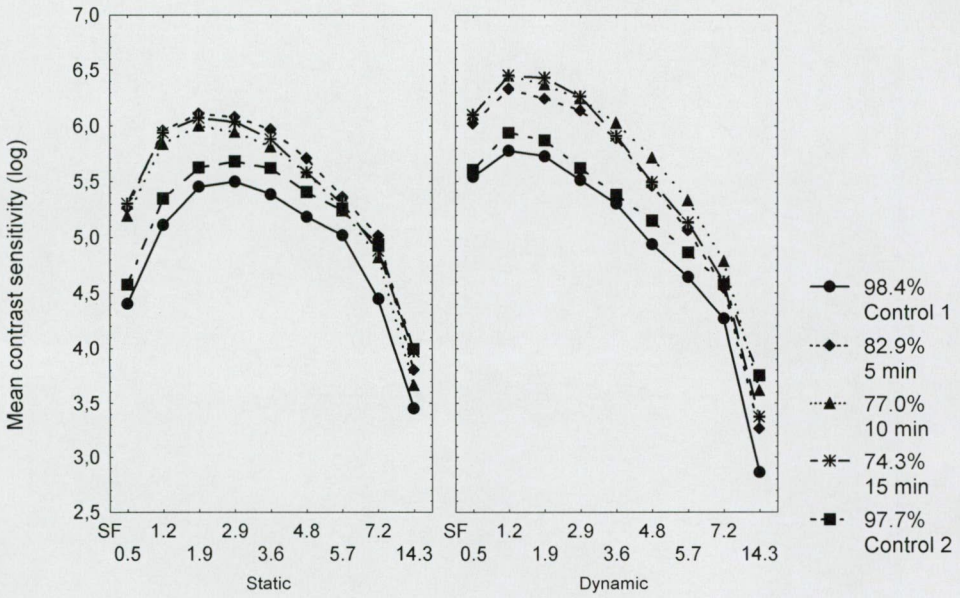

Fig. 1. Mean static and dynamic visual contrast sensitivity (VCS) in hypobaric hypoxic states and in two control conditions. The duration of hypoxic exposure and the corresponding mean arterial blood oxygen saturation are also shown.

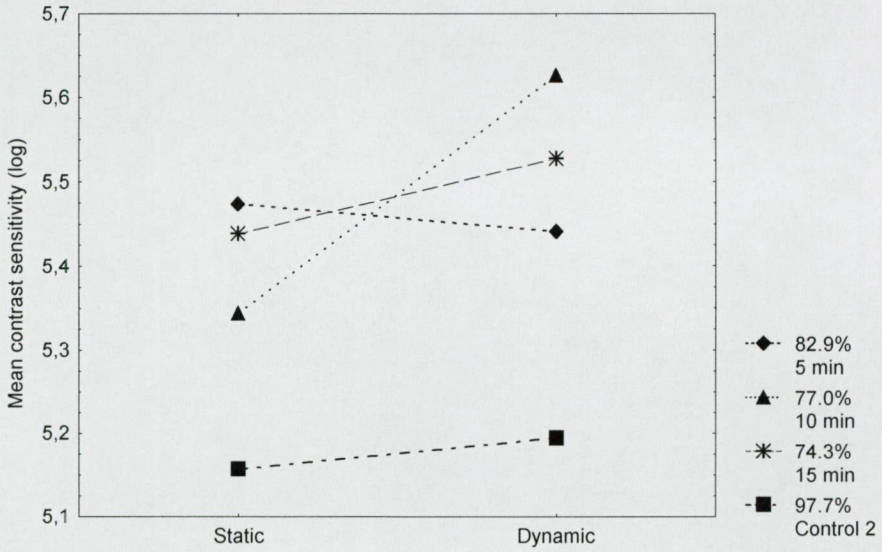

Fig. 2. Static and dynamic visual contrast sensitivity from the hypoxic and control conditions. Data are collapsed across the spatial frequencies tested. The duration of hypoxic exposure and the corresponding mean arterial blood oxygen saturation are also shown.

Study 3.

Spatial contrast sensitivity of migraine patients without aura

Abstract

Visual disturbances are frequent symptoms in migraine. Since there is a possibility of separate damage in the magno- or parvocellular visual pathway in migraine patients, we performed a study including the assessment of static and dynamic spatial contrast sensitivity on 15 common migraine patients under photopic and scotopic conditions. Fifteen healthy volunteers without primary headache served as controls. The results revealed a marked decrease in contrast sensitivity at low spatial frequencies in the migraine patients, although static stimulation under photopic conditions also indicated a slight decrease also at higher frequencies. Contrast sensitivity demonstrated a marked lateralization, as the sensitivity to low spatial frequencies obtained through the eye on the symptomatic side was significantly inferior to that obtained through the fellow eye.

These findings suggest that the mechanisms responsible for vision at low spatial frequencies are impaired in migraine patients. This suggests an impaired function of the magnocellular pathways in this disease.

Introduction

Visual symptoms are common in migraine. The most striking ones appear in the aura, frequently involving with transitional blurred vision, homonymous hemianopsy, scotomas or photophobia (for reviews, see Chronicle & Mulleners 1996, Schoenen 1998). These phenomena obviously signal the involvement of visual retino-cortical mechanisms in the pathophysiology of migraine. The major question still remains, however, of whether the parallel parvo- and magnocellular visual pathways are equally affected in this condition or there is a preponderance of magnocellular malfunctions in migrain-associated visual phenomena (Coleston et al. 1994, Khalil 1991). The answer to this question is greatly hindered by the difficulty in distinguishing between magnocellular and parvocellular dysfunctions in human clinical investigations (Bassi & Lehmkuhle 1990). Nevertheless, it is generally held that the parvocellular pathway dominates in the information transfer at high spatial frequency (SF) and low temporal frequency (TF), while the magnocellular pathway

conveys information at low SF and high TF (Shapley et al. 1982, Merigan et al. 1993). This warrants the application of contrast sensitivity measurements in migraineurs.

The use of scotopic stimulating conditions was indicated by animal experiments in which visual stimulation at low SFs and under scotopic conditions excited predominantly magnocellular ganglion cells in the retina (Purpura et al. 1988, Lee et al. 1997). Scotopic tests have been employed in several human studies in the search for pathological alterations in human magnocellular functions (Schefrin et al. 1999, Drum et al. 1986). With regard to these facts, we set out to compare photopic and scotopic spatial contrast sensitivity functions in migraine patients without aura. To increase the sensitivity of these examinations, both static and dynamic contrast sensitivity functions were tested.

In this study we employed both monocular and binocular testing. This approach could provide data to the major question of whether the altered visual processing in migraine patients is due to cortical or precortical mechanisms (Coleston et al. 1994). Electrophysiological experiments indicated some visual interictal abnormalities in migraine, related to the laterality of the visual aura (van der Kamp et al. 1996). In this regard the appearance of an interocular asymmetry in spatial contrast sensitivities might be of considerable theoretical importance.

Subjects and methods

The patients enrolled in the study were 15 women with common migraine. The visual acuity was 1.0 in all cases. The age-range was 18-53 years, with a median age of 31 years. The duration of the illness ranged between 1 and 25 yrs, with a median value of 10 years. The patients were diagnosed according to the criteria of the International Headache Society (1988). All subjects underwent detailed neuro-ophthalmological examinations, including physical examination, CAT scan, blood chemistry, ophthalmoscopy and visual perimetry. Only patients with no other neurological or ophthalmological diseases were included in the study. The control group comprised 15 age-matched female volunteers with good vision and without neurological symptoms or primary headache.

Results

Spatial contrast sensitivity functions revealed considerable deviations in migraine patients (Fig. 1). These were most marked at sensitivities measured at low SFs and under scotopic conditions. Photopic spatial contrast sensitivity functions failed to show significant

differences between the eyes on the symptomatic and the non-symptomatic side of migraine patients when tested with static visual stimuli. However, significant differences ($F = (1,28)$ 7.34, $p < 0.05$) were detected only when sensitivities in the low SF range were compared (between 0.5 and 3.6 cycle/degree).

Similarly, when the contrast sensitivity functions for the symptomatic eyes of the patients were compared with the right eyes of the control subjects, no difference was found. Again, when the contrast sensitivities in the low SF range were compared, highly significant differences were detected ($F = (1,25)$ 55.749 $p < 0.0001$). Similarly significant differences in sensitivity were seen between the non-symptomatic eyes of migraineous patients and the left eyes of the control subjects ($F=(1,25)$ 21.929, $p<0.0001$).

Under photopic dynamic conditions the static contrast sensitivity values indicated similarly significant differences in the low SF range between the symptomatic and the non-symptomatic side of the migraineous patients ($F = (1,27)$ 13.04, $p<0.005$). When the values obtained over the eyes on the symptomatic side of the migraineous patients were compared with those obtained over the right eyes of the control subjects, ANOVA demonstrated highly significant differences ($F=(1.27)$ 105.28, $p<0.0001$). The differences between the non-symptomatic eye of the migraineous patients and the left eyes of the control subjects were also significant ($F = (1,20)$ 71.053, $p < 0.0001$).

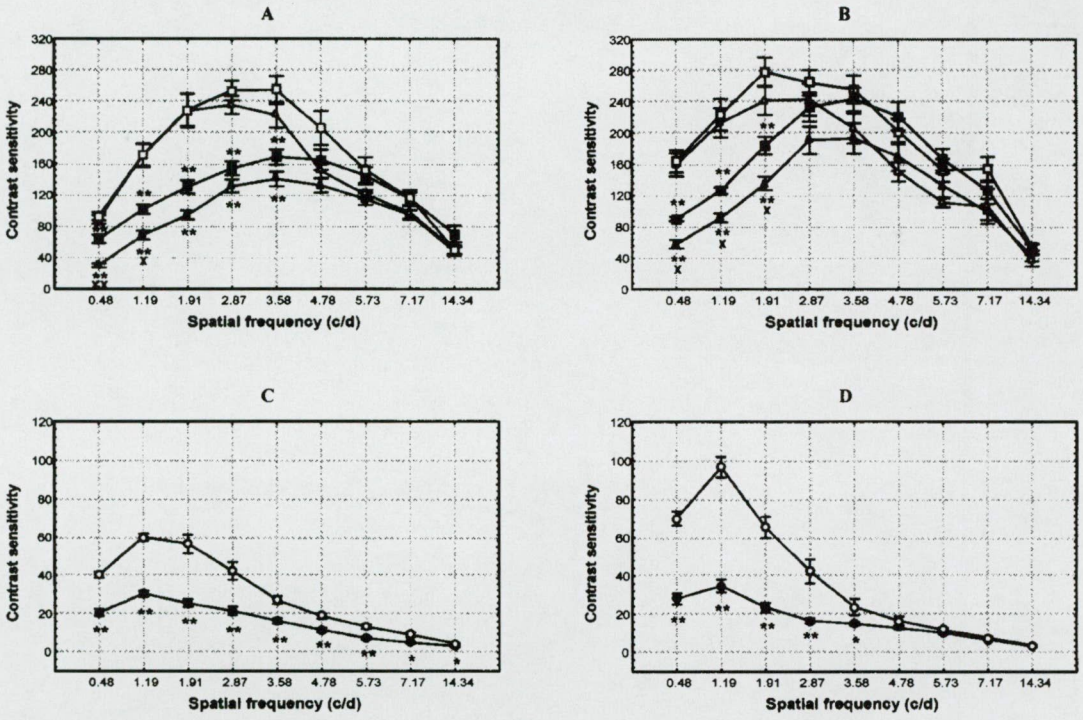

Fig. 1. Spatial contrast sensitivity functions of migraine patients and control subjects (A) photopic contrast sensitivity estimated by static stimulation and (B) photopic contrast sensitivity functions estimated by dynamic method. Control subjects, open symbols; migraine patients, filled symbols; ■, □, through the more sensitive eye, ▲, and Δ through the less sensitive eye. (C) scotopic spatial contrast sensitivity estimated by static stimulation and (D) scotopic spatial contrast sensitivity estimated by dynamic stimulation. Control subjects ○, migraine patients ●, * and ** mark significant differences to the corresponding eyes of control subjects on the 0.05 and 0.001 probability levels, respectively. x and ** denote significant interocular contrast on the 0.05 and 0.001 probability levels, respectively. Values are shown as mean ±S.E.M.

Under scotopic conditions, only the binocular spatial contrast sensitivities were compared in both the static and in the dynamic tests. Under these conditions, spatial contrast sensitivity functions with low-pass filter characteristics were obtained. Accordingly, significant differences were found between the migraineous and control spatial contrast sensitivity values in the dynamic test both in the low SF range ($F= (1,23)\ 92.29$, $p<0.0001$), and over the whole SF range between 0.5 and 3.6 cycle/degree. Similarly significant differences were seen in the static tests under scotopic conditions. Since the contrast sensitivity in the low SF range dominates in these curves, ANOVA showed similarly highly significant differences both in the low SF range ($F= (1, 23)\ 87.23$, $p<0.0001$) and over the whole range of frequencies tested ($F= (1,23)\ 89.64$, $p<0.0001$).

Discussion

Our results show significant changes of spatial contrast sensitivity in patients with migraine without aura. A particularly noteworthy reduction was found in the low SF range. In view of the well-known dominance of the magnocellular pathway in the transmission of visual information in the low SF range (Shapley et al. 1982, Merigan et al. 1993), this may suggest impaired magnocellular visual functions in migraine patients. The finding that the decrease in the contrast sensitivity in the migraine patients was especially marked under scotopic circumstances further substantiates this evidence. The magnocellular ganglion cells in the retina (Kaplan & Shapley 1986) and in the dorsal lateral geniculate nucleus (Derrington et al. 1984, Hicks 1983), and the cells in layer 4C (Hawken 1984) display a similar contrast sensitivity function to that observed in humans under scotopic circumstances. There is other evidence, too that the scotopic vision is impaired after magnocellular damage (Drum et al. 1986, Wolf et al. 1996). Our finding therefore seems to support the notion that there could be an asymmetric disturbance in the function of the parallel visual pathways of migraine patients without aura. The temporal contrast sensitivity in migraine patients has already been studied and, in concert with our conclusions, a definite reduction of this function in migraine with aura has been found (Khalil 1991).

It remains to be settled whether the weaker contrast sensitivity at low SF represents a cortical or precortical mechanism. It is interesting from this respect that we found significant interocular side differences in the interictal measurements of contrast sensitivity in the migraine patients. This provides evidence for a retinal manifestation of the pathophysiological processes accompanying migraine. Several factors could cause the retinal symptoms in these conditions. The first could be asymmetry of the ocular blood perfusion in migraine patients. However, no data are available on retinal perfusion in this disease group. The second factor that could explain the interocular differences is asymmetry in the neuromodulator functions of the eyes. Dopamine could be a candidate for this since it is produced in abundance in the retina, predominantly in the amacrine cells of the outer plexiform layer (Frederick et al. 1982, Pourcho 1982). Interictal hypersensitivity of the dopamine receptors was earlier described in migraine patients (see the review by Mascia et al. 1998) and magnocellular visual deficits have been reported in Parkinson's disease (Bodis-Wollner & Yahr 1978). Thus, dopaminergic mechanisms might be responsible for the predominance of magnocellular defects observed in migraine patients. Besides dopamine several other neuromodulator mechanisms could also be responsible for the pathological functions during migraine. Both the excitatory substance P

and the vasodilatator CGRP have been stated to be produced by different subtypes of amacrine cells (Cuenca & Kolb 1998, Kiyama et al. 1985, Morgan et al. 1994, Boelen et al. 1994, Boelen 1991). Nevertheless, no migraine-related interocular asymmetry in any neuromodulator functions is available to substantiate this hypothesis.

The findings that there is an eye to eye side-difference in the contrast sensitivity of migraine patients is certainly not in contradiction with the known interhemispheric differences in a series of parameters, including visual evoked potential studies measured interictally or ictally in migraine patients (Boles 1993, Boiardy et al. 1988). The interocular and interhemispheric differences could represent two independent pathophysiological processes or, alternatively, could be in relationship with the dominance of contralateral eyes in determining hemispheric responses (Barett et al. 1976). The visual evoked potential studies by Tagliati et al. (1995) and Shibata et al. (1997) demonstrated significant side differences in hemianopic migraine aura. The evoked potential studies by Oelkers et al. (1999) presented evidence for interictally persisting dysfunctions of the precortical visual processing in interictal conditions. Positron emission tomography, however, failed to indicate any side difference during the visual aura of classic migraine, while there was a 40% overall decrease in the regional cerebral blood flow (Diener 1999). At any event, the interocular differences in contrast sensitivity can be regarded as evidence for a precortical site of action in the pathophysiology of this disease, a hypothesis raised earlier (Coleston et al. 1994). Cortical afflictions in migraine patients have already been widely described. Studies on retinal or optic tract abnormalities, however, are rather rare. Our findings lead us to suggest that a thorough investigation of the visual phenomena accompanying migraine might promote our knowledge concerning the pathomechanism of this painful condition.

Study 4.

Impaired visual contrast sensitivity and concentrically narrowed visual fields in headache patients with primary empty sella syndrome

Abstract

The aim of the study was to assess visual deficits in patients with primary empty sella syndrome. Altogether 15 cases of primary empty sella syndrome were diagnosed in the clinical workup of continuous holocranial headache during the last 5 years. These patients had predominantly preserved visual acuity did not show any major neurological deficits. Detailed neuro-ophthalmological evaluation including automated visual contrast sensitivity measurements and automated perimetry, rather uniformly demonstrated signs of visual deficits characterized by impaired contrast sensitivity and concentric narrowing of the visual field. These findings indicate that empty sella syndrome may lead to visual symptoms similar to those observed in benign intracranial hypertension.

Introduction

The diagnosis of primary empty sella syndrome (ESS) is based on radiological findings characterized by an arachnoid herniation filled with liquor that compresses the pituitary against the sellar wall (Sage et al. 1980, Spaziante et al. 1981). ESS occurs particularly in obese, hypertensive women (Jordan et al. 1977); it is often asymptomatic but it may be associated with ophthalmologic, neurologic and sometimes non-characterizing endocrine disorders (Guinto et al. 2002, McFadzean 1983, Braatvedt & Corall 1992). Neuro-ophtalmological aspects of ESS, however has not yet been previously studied.

We report here 15 cases of primary ESS that had been referred to our electrophysiological laboratory because of continuous holocranial headache without any major neurological deficits or ophthalmological signs.

Methods

Clinical data on a total of 15 ESS patients (11 women and 4 men) are presented here (Table I). Their ages ranged between 21 and 74 yrs (mean: 49.87 yrs). All these patients had presented at the neurological department because of their continuous holocranial headache, which greatly interfered with their daily life.

No	Name	Gender	Age at conclusion yrs	Length of visual symptoms in yrs	Visual acuity with correction		Visual field deficit residual deg		Intraocular pressure Hgmm		Accompanying diseases or symptoms
					R	L	N	T	R	L	
1.	T. Sz.	♀	66	3 yrs	0.6	0.5	10	10	18	18	Hypertension, diabetes, glaucoma
2.	K. S.	♀	44	5 yrs	1.0	1.0	30	50	16	16	Diabetes, hypertension
3.	E. A.	♀	21	3 yrs	1.0	1.0	15	20	14.5	18	Pituitary adenoma
4.	H. I.	♂	53	5 yrs	1.0	1.0	40	60	20	20	Amaurosis fugax
5.	T. M.	♀	74	5 yrs	0.5	0.5	30	30			Ischaemic cerebropathy
6.	V. S.	♀	52	8 yrs	0.8	lp	5	5	20	12	Glaucoma
7.	Cs. A.	♀	52	5 yrs	1.0	1.0	15	20	18	17	
8.	T. S.	♀	44	4 yrs	1.0	1.0	20	20			
9.	C. L.	♀	47	4 yrs	1.0	1.0	10	10			
10.	S. F.	♂	46	6 yrs	1.0	1.0	20	20	18	20	
11.	B. E.	♀	53	5 yrs	1.0	hmp	20	20	17	17	Arachnoid cyst
12.	H. S.	♀	53	6 yrs	1.0	1.0	10	15	14	17	Early hair graying
13.	M. I.	♂	46	4 yrs	1.0	0.8	40	50	21	26	
14.	F. I.	♂	57	7 yrs	1.0	0.8	5	5	20	18	
15.	P. Gy.	♀	40	6 yrs	1.0	1.0	10	10	14	16	Vertigo, postural Hypacusis

All underwent a battery of routine neurological physical examination procedures. Radiological examination included MRI recordings of the brain, which in all cases proved the diagnosis of ESS. Ophthalmological examination consisted of ophthalmoscopy, the recording of visual acuity, the assessment of intraocular pressure and visual perimetry with a Tuebingen perimeter. Electrophysiological tests (electroretinogram and visual evoked potentials) were performed according to the ISCEV standards.

The control group comprised 15 age-matched female volunteers with good vision who had no history of any neurological illness or primary headache.

Results

Ophthalmological findings

All patients had visual complaints, such as transient visual loss or blurring of vision, which had been going on for 3 to 8 years (mean: 5.1 yrs). Visual acuity was generally good or only mildly impaired (corrected visual acuity was 1.0 in 21 of the 30 eyes of the 15 patients, 0.8 in 3 eyes, and 0.5-0.6 in 4 eyes. In 2 patients, only residual light sensitivity (hand-movement perception or light perception was found in one eye, with rather good vision (1.0 and 0.8) in the contralateral eye. The reason for this impairment was retinal ablation in one case and amaurosis fugax in the other (Table I.).

The intraocular pressure was found to be in the normal range in all but one case. Ophthalmoscopic examination revealed no pathological signs in most of the cases (13 of the 15). Mild papilledema was found in one case, and a decolored papilla in another.

Neurological findings

All patients 15/15 (100%) had continuous, holocranial headache. Otherwise no neurological signs were observed.

Co-morbidity

Eight of the 15 patients had mild medically compensated accompanying diseases, including diabetes (N=2; 13%) glaucoma (N=2; 13 %) and hypertension (N=7; 46%). Detailed clinical data about medications are included in table 1.

Electrophysiological findings

The ERG and visual evoked potentials were normal in all cases. All the patients exhibited a considerable deficit of the visual field, characterized mostly by a concentric narrowing. The visual field was constricted to a radius of 10^{o} or smaller in 6 cases, 20^{o} or smaller in 4 cases, and 30^{o} in 4 cases; in one case the total lower hemifield was defective.

Contrast sensitivity

Both the photopic and the scotopic visual spatial contrast sensitivity revealed deterioration in all patients. The average photopic visual spatial contrast sensitivity proved to be decreased at all SFs. ANOVA demonstrated significant differences between the values obtained in the patient group versus those in the control group ($p<0.001$). The post-hoc comparison revealed

a significant impairment of the contrast sensitivity in the patient group at all SFs examined ($p<0.01$) (Fig., 1A).

The scotopic contrast sensitivity functions similarly indicated a significant effect of the pathological conditions. ANOVA furnished significant differences between the patient and control group values ($p<0.001$). Post-hoc analysis likewise yielded significant differences between the values obtained on the patients and on the control group ($p<0.001$) (Fig. 1B).

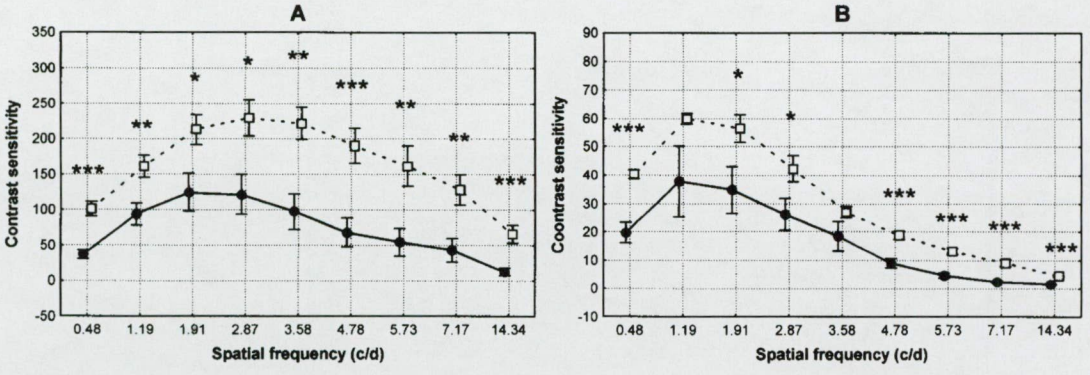

Fig. 1. Photopic (A) and scotopic (B) spatial visual contrast sensitivities in the patient group (●) and control group (□). Abscissa: spatial frequency values in cycles/degree. Ordinate: Visual spatial contrast sensitivities. Vertical bars indicate standard error of mean (S.E.M) values. Asterisks indicate significance values at 0.05 (∗), 0.01 (∗∗) or 0.001 (∗∗∗) level.

Discussion

Our results showed that the group of headache patients with primary ESS displayed characteristic, consistent visual deficits, and impaired visual spatial contrast sensitivities. Such an impairment of the visual spatial contrast sensitivity is in contrast with the preserved visual acuity of these patients, who otherwise might have definitive visual complaints.

The decreased contrast sensitivity was in most cases accompanied by severely and concentrically constricted visual fields. Earlier clinical reports on ESS emphasised mostly its radiological (Sage et al. 1980), neurosurgical or endocrinological aspects (Jordan et al. 1977). Relatively few studies have dealt with its relationship to visual and neurological aspects. In some cases severe visual field defects have been described in ESS patients, that was localized characteristically to the upper temporal quadrant (Fusco et al. 1988); other reports did not

mention visual field defects, but sometimes mild visual symptoms (see Braatvedt & Corall 1992 for a survey). No detailed study has previously been performed on headache patients with clinically diagnosed ESS by using modern visual techniques such as automated perimetry combined with computer-supported contrast sensitivity measurements. No study at all has dealt with the scotopic vision of these patients either. These could be reasons why the association of these two phenomena has not been revealed earlier.

Our perimetry studies demonstrated predominantly a concentric narrowing of the visual field. This type of visual defect has repeatedly been reported earlier in patients with benign intracranial hypertension, though in only a small proportion of the cases (Brodsky et al. 1998). Concentric narrowing of the visual field is usually regarded as a rare, but serious side effect of Vigabatrin treatment (Lawden et al. 1999). This phenomenon is also known to occur in other diseases, such as hysteric amblyopia (Sletteberg et al. 1989, Berman & Levi 1975), optic atrophy (Amemiya & Honda 1994, Miki et al. 1997) and after trauma-based brain injuries (Langerhost & Safran 1998).

We propose that the alteration of contrast sensitivity, the constricted visual fields and the axonal damage might be due to direct or indirect effect of intracranial hypertension. This hypothesis is confirmed by several previous research findings, while ESS is often associated with a transient or continuous increased intra cranial pressure (Davis et al. 1978, Foley 1975, de Vries Knoppert 1986, Takanashi et al. 2001, Britton et al. 1980, Weisberg 1985). There is evidence from animal studies concerning the effect of direct compression on the anterior visual system, though there are conflicting reports as to which fiber type is most susceptible. In the cat, on optic nerve pressure block has been shown to selectively disrupt large-diameter (magnocellular) fibers (Burke et al. 1998). Reese and Cowey (1989) found, however, that a suprasellar meningioma in a macaque monkey, which compressed the optic nerves, chiasm and tracts dorsally, caused a selective loss of smaller diameter (parvocellular) fibers. In our cases, the contrast sensitivity was decreased in almost the whole SF range studied. Hence, our observations do not support any selective lesion of either the magno- or the parvocellular pathway in this group of patients with ESS. This is in line with the report of Gutowski et al. (1997) on patients with suprasellar meningeomas. During our observation period none of our patients displayed any clinical signs of increased intracranial pressure besides headache. The optic tract lesion, however, is typical of those reporting increased intra cranial pressure in their case history. This strengthens the conclusion that increased local intra cranial pressure could play an important role in the patomechanism of ESS and the presence or severity of visual symptoms could be the measure of different stages of the disease.

Discussion

Overview on the parallel processing of visual information.

The classical view on visual pathways used a rather simplified scheme that originated from the retina was relayed in the lateral geniculate body and projected to the primary visual cortex. These schemes had been accepted generally, since Schultze (1866) described the duality of vision theory in the XIXth century based on his observations concerning scotopic and photopic vision. Now the parallel processing of visual information is a term used in the context that different properties of the visual scene are analysed concurrently and to some degree independently. Several separate lines of thought promoted our ideas about the parallel organization of vision.

1. Trevarthen (1968) and Schiller (1969) published independently their theory on the duality of vision based on animal experiments. Schiller's theory was based on the separation of tectal and geniculocortical visual information. This duality exists already on certain levels of phylogenesis, although tectal vision emerges rather often even in human context. Schiller (1968) proved in his experiments with hamster that tectal and geniculo-cortical pathways processes different information context. Trevarthen (1969) based his theory on the duality of focal and ambient vision. Focal vision exists in diurnal primates. It represents a detailed visual representation with high angular resolution (minute of arc). The focal vision is sensitive to position, orientation, luminance or hue. It is also called foveal, since its appearance is connected to the appearance of fovea in the phylogenesis. The ambient vision of Trevarthen (1969) is also called global vision. It is characterized by low angular resolution for stationary features and low sensitivity to relative position, orientation, luminance or hue. In contrast to these there exist a high sensitivity to change in these parameters. Peculiarity of the ambient (global) vision is that there is little change under scotopic conditions.
2. Parallel processing of visual information is based on the existence of different neuronal groups in the retina, in the lateral geniculate body (CGL) and in the cortex. The neuronal groups of different sizes are associated with axonal classes of different sizes. Crucial observation was in context to this that neurons of different sizes are ordinarily connected to the neurons of the same size. Based on these the X, Y and W classes of cells have been found in the cat visual system and M(agnocellular), P(arvocellular) and K(oniocellular) neuron classes have been described in primates.

3. Human pathological cases suggest that certain functions are connected to circumscribed regions of the cerebral cortex. Typical example is the phenomenon of prosopagnosia, i.e. the inability of certain individuals to recognize faces while having no trouble in any other fields of visual processing. This means that there is a parallel processing of sensory information at least in the cortico-cortical processing.
4. Ungerleider and Mishkin (1982) described a "dorsal" and a "ventral" stream of visual information processing based upon imaging studies. They proved e.g. that visual functions in connection to visual stimulus localization are performed predominantly by parietal cortical areas, while tasks aiming at recognition of familiar objects activate predominantly temporal visual areas (like the inferotemporal cortex)

Since the subject of the dissertation concerns mainly the distinction between neuronal groups based upon their size, in the following we detail the physiological properties in connection to this distinction. Already Cajal recognised in 1893 the morphological diversity of retinal cells. Polyak (1941) classified retinal cells by the size and by the size and shape of the dendritic tree. Although the functional heterogenity of ganglion cells was emphasised by Granit (1955) in his early works on cat and frog retinas, the concept of parallel processing aroused little interest until Enroth-Cugell & Robson (1966) characterized the X- and Y-cells of the cat. The discovery of W-cells is attributed to Hoffmann and Stone (1985). The crucial point in discovering parallel visual pathway was that large cells in the retinal are exclusively connected to large cells in the geniculate body and so on.

The existence of separate visual pathways in the primate brain has been proved by both anatomical and physiological methods (for reviews see Lennie 1980 and Shapley 1990).

A couple of physiological functions are sensitive to distinctions between X, Y and W or M, P and K cells including spatial contrast sensitivity function (CSF), temporal contrast sensitivity function (CSF), velocity sensitivity, visual responsive transience and chromatic sensitivity.

The large cells of the cat are designated as Y-cells, while those in primates are named as M (magnocellular) cells, the terms: Y-like or parasol cells are similarly widely used. Their receptive field diameter is rather large which is associated with a low spatial resolution ability and linearity in spatial summation. In contrast, large cells exhibit higher contrast sensitivity and temporal resolution than other types of visual cells. The visual responses of these cells are of phasic character. These large cells whenever they located have the unique properties that are specifically sensitive to motion.

The medium-cells of the cat include X, cells, while this type of cells is called P (parvocellular) in primates. In some context either the term X-like or midget is used. These

cells are characterized by small receptive field diameter, high spatial resolution, relatively low contrast sensitivity and temporal resolution and tonic response to stimulation. In some species chromatic opponency have also been observed by these cells.

Finally, the small cells in the cat visual system have been designated as W cells. In primates the term K (koniocellular) or W-like cells is used. These cells have large receptive field diameters, they show low maintained activity and slow conduction velocities (due to their thin myelin sheath). The visual onset latencies of the cells are long.

Overview of our results

The importance of the parallel visual pathways has been accentuated by reports that certain human pathological processes damage selectively either the magnocellular or the parvocellular pathway (Bassi & Lehmkuhle 1990; Demb et al. 1998; Steinman et al. 1998; Vogt et al. 1998; Vidyasagar & Pammer 1999). The functional characteristics make the classification of the differing neuronal populations fairly easy, provided the possibility is to record single-unit activity. The situation is much more complicated if we are looking for physiological or pathophysiological mechanisms in connection to parvo- or magnocellular activity at behavioural level.

What are the methodological means to distinguish between parvocellular and magnocellular visual activity in humans?

The use of isoluminant chromatic stimuli seems to be reasonable and proved to be useful in detecting parvocellular functions. More difficulties arose with magnocellular ones. Several attempts have been made to clarify the human magnocellular functions. Various techniques and mathematical procedures have been used to assess the relative contribution of visual evoked potentials originating from the underlying magnocellular neural mechanisms (Conte et al. 1983; Thompson & Drasdo 1992; Baseler et al. 1995; Klistorner et al. 1997; Valberg & Rudvin 1997). Similarly, specific stimulation techniques have been introduced. Thus, apparent movement stimulation and motion onset stimulation have been employed in some physiological and clinical studies (Kubova et al. 1995; Tobimatsu et al. 1995). Likewise, light flickering at high frequency and low-contrast has been repeatedly used to distinguish between magnocellular and parvocellular functions (Regan 1973, 1989, Nakayama & Mackeben 1982; Kulikowski 1991, Fiorentini et al. 1991, Regan & Lee 1993; Klistorner et al. 1997). Pammer & Whatley (2001) have introduced the illusion produced by spatial frequency doubling.

Recently, recognition of vernier stimuli has been added to these methods (McKendrick et al. 2002).

In our studies we succeeded in proving the overlap of scotopic contrast sensitivity at low spatial frequencies with magnocellular functions. Our results seem primarily important from the methodological viewpoint. Although, Purpura et al. (1988) recognised that only magnocellular neurons serve retinal information processing under scotopic conditions in monkeys no human study has been devoted to this problem. The only piece of data is that scotopic contrast sensitivity has been found decreased among glaucoma patients (Congdon et al. 1995). Our results provided evidence for the close connection between magnocellular neural activity and scotopic vision. Both psychophysiological and electrographic data support this relationship. The relationship is striking when we compare human scotopic contrast sensitivity contrast sensitivity of magnocellular retinal neurons. Further, the method proved to be sensitive for detecting the selective magnocellular damage in migraine patients and its absence of patients with empty sella.

Our results, thus, suggest a rather sensitive and potentially objective approach to indicate magnocellular damage in humans and offer a new methodological tool in the investigation of magnocellular functions under clinical circumstances. Only the long dark-adaptation seems to be a limiting factor in this aspect, because it makes testing tedious and time-consuming. Still, in our migrain study we demonstrated the superiority of scotopic oriented methods in detecting magnocellular damage.

Even in the absence of a sensitive method there are numerous data available on selective parvo- or magnocellular damage in various pathological conditions. Magnocellular neurons seem to be especially sensitive to increased pressure, hypoxia (Lennie 1980, Bassi & Lehmkuhle 1990), senility (Schefrin et al. 1999) and potentially other conditions. First magnocellular damages due to increased perineural pressure have been recognised. Magnocellular damage has been recognised in glaucoma (Klistorner & Graham 1999) and in sellar or orbital tumours (Janáky & Benedek 1992). However, this hypothesis has been, severely criticised as glaucomatous neural damage concerns. There are several reports on magnocellular damage in schizophrenia (McClure et al. 2001, Butler et al. 2001, Schwartz et al. 1999). The selective magnocellular damage in Alzheimer disease or in Parkinson disease is questionable (Regan & Maxner 1987, Arakawa et al. 1999). Similarly, there are reports for and against the selective magnocellular damage in dyslexic patients (Pammer & Wheatley

2001). Selective magnocellular damage has been described originally in melanoma-associated retinopathy. Although later selective damage of bipolar retinal cells has been revealed. Selective parvocellular damage has been reported in certain forms of amblyopia (Shan et al. 2000) and in some cases of multiple sclerosis and retinitis pigmentosa.

This list of disease conditions clearly shows that magnocellular damage in human patients is a multifactorial Pathopysiological entity. It is interesting from this aspect that hypobaric hypoxia selectively activated mechanisms connected to magnocellular systems in our experiments. Our study was the first, detecting early activation of magnocellular mechanisms under hypobaric hypoxia. Certainly, longer exposure to the same challenge leads to impairment and damage of the same systems. Nevertheless, our results offer a new way of investigating magnocellular functions.

Our clinical studies served with rather interesting results. Two major disease categories have been approached in our studies. While, definitive magnocellular impairments have been detected in migraine patients without aura, no signs of selective magnocellular damage have been detected at patients with empty sella and headache. This contrast is interesting, because migraine patients were devoid of visual symptoms, while empty sella patients displayed concentric narrowing of the visual field, which suggest definitive visual defects.

Further studies with a wide variety of patients with headache are needed to clarify this seemingly contradictory data.

Conclusions

1. Our results provided psychophysiological and electrophysiological evidences for the use of scotopic contrast sensitivity as a tool in the clinical investigation of magnocellular visual functions. We suggest that the decrease of scotopic contrast sensitivity reflects impairments of the magnocellular visual pathways.
2. Our results revealed a hitherto unknown effect of hypoxic hypoxia on visual contrast sensitivity. Under hypobaric (1/2 atm) conditions contrast sensitivity shows significant improvement in the low spatial frequency range.
3. Definite contrast sensitivity impairment was observed in the low spatial frequency range of contrast sensitivity of migraine patients without aura. These results suggest that the pathomechanism of migraine affects selectively the parallel visual pathways.

4. Significant contrast sensitivity impairment in the whole spatial frequency range and concentric narrowing of the visual field was observed in headache patients with primary empty sella syndrome. These results suggest precaution in the handling of visual symptoms of patients with empty sella syndrome.

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References

1. **Alexander KR, Pokorny J, Smith VC, Fishman GA, Barnes CS.** Contrast discrimination deficits in retinitis pigmentosa are greater for stimuli that favor the magnocellular pathway. Vision Res 2001 41: 671-683.
2. **Amemiya T, Honda A.** A family with optic atrophy and congenital hearing loss. Ophthalmic Genet 1994 15: 87-93.
3. **Arakawa K, Tobimatsu S, Kato M, Kira J.** Parvocellular and magnocellular visual processing in spinocerebellar degeneration and Parkinson's disease: an event-related potential study. Clin Neurophysiol 1999 110: 1048-1057.
4. **Barett G, Blumhardt L, Halliday AM, Halliday E, Kriss A.** A paradox in the lateralisation of the visual evoked response. Nature 1976 261: 253-255.
5. **Barnard N, Crewther SG, Crewther DP.** Development of a magnocellular function in good and poor primary school-age readers. Optom Vision Sci 1998 75: 62-68.
6. **Bartholomew CJ, Jensen W, Petros TV et al.** The effect of moderate levels of simulated altitude on sustained cognitive performance. Int J Aviat Psychol 1999 351-359.
7. **Baseler HA, Bearse MA, Sutter EE.** P/M channel ratio as a function of eccentricity revealed by a decomposition of the human VEP. Invest Ophthalmol Vis Sci 1995 36: S942.
8. **Bassi CJ, Lehmkuhle S. Clinical implications of parallel visual pathways.** J Am Optom Assoc 1990 61: 98-110.
9. **Benedek G, Janáky M, Adamkovich N, Rubicsek G, Sáry G.** Scotopic pattern-reversal visual evoked potentials. Clin Vision Sci 1993 8: 47-54.
10. **Berman MS, Levi DM.** Hysterical amblyopia: electrodiagnostic and clinical evaluation. Am J Optom Physiol Opt 1975 52: 267-274.
11. **Bodis-Wollner I. Yahr MD.** Measurements of visual evoked potentials in Parkinson`s disease. Brain 1978 101: 661-671.
12. **Bodis-Wollner I, Onofrj MC, Marx MS, Mylin LH.** Visual evoked potentials in Parkinson's disease: spatial frequency, temporal rate, contrast and the effect of dopaminergic drugs. In Cracco RQ, Bodis-Wollner I. (Eds.), Evoked Potentials New York: Alan R. Liss. 1986 pp. 307-319.
13. **Boelen MK, Wellard J, Dowton M, Chubb IV, Morgan IG.** Glycinergic control of (leu5)enkephalin levels in chicken retina. Brain Res 1991 557: 221-226.

14. **Boelen MK, Wellard J, Dowton M, Morgan IG.** Endogenous dopamine inhibits the release of enkephalin-like immunoreactivity from amacrine cells of the chicken retina in the light. Brain Res 1994 645: 240-246.
15. **Boiardy A, Frediani F, Leone M, Munary I, Bussone G.** Cluster headache: lack of central modulation? Funct Neurol 1988 3: 79-87.
16. **Boles DB.** Visual field effects of classical migraine. Brain Cogn 1993 21: 181-191.
17. **Bowers F, Valter K, Chan S et al.** Effects of oxygen and bFGF on the vulnerability of photoreceptors to light damage. Invest Ophthalmol Vis Sci 2001 42: 804-815.
18. **Braatvedt GD, Corrall RJ.** The empty sella syndrome: much ado about nothing. Br J Hosp Med 1992 47: 523-525.
19. **Britton C, Boxhill C, Brust JC, Healton EB, Braun CW, Killian P.** Pseudotumor cerebri, empty sella syndrome, and adrenal adenoma. Neurology 1980 30: 292-296.
20. **Brodsky MC, Valhiades M.** Magnetic resonance imaging in pseudotumor cerebri. Ophthalmology 1998 105: 1686-1693.
21. **Burke W, Dreher B, Wang C.** Selective block of conduction in Y optic nerve fibres: significance for the concept of parallel processing. Eur J Neurosci 1998 10: 8-19.
22. **Butler PD, Schechter I, Zemon V, Schwartz SG, Greenstein VC, Gordon J, Schroeder CE, Javitt DC.** Dysfunction of early-stage visual processing in schizophrenia. Am J Psychiatry 2001 158: 1126-1133.
23. **Caine D, Watson JD.** Neuropsychological and neuropathological sequelae of cerebral anoxia: a critical review. J Int Neuropsychol Soc 2000 6: 86-99.
24. **Cajal, S R.** (1892) The Structure of the Retina. Translated by S.A. Thorpe and M. Glickstein, Springfield, Il., Thomas, 1972.
25. **Campbell F.** Why do we measure contrast sensitivity? Behav Brain Res 1983 10: 87-97
26. **Caruana PA, Davies MB, Weatherby SJ, Williams R, Haq N, Foster DH, Hawkins CP.** Correlation of MRI lesions with visual psychophysical deficit in secondary progressive multiple sclerosis. Brain 2000 123: 1471-1480.
27. **Chronicle EP, Mulleners WM.** Visual system dysfunction in migraine: a review of clinical and psychophysical findings. Cephalalgia 1996 16: 525-535.
28. **Coleston DM, Chronicle E, Kennard C.** Pre-cortical dysfunction of spatial and temporal visual processing in migraine. J Neurol Neurosurg Psychiatry 1994 57: 1208-1211.

29. **Congdon NG, Quigley HA, Hung PT, Wang TH, Ho TC, Glovinsky Y.** Impact of age, various forms of cataract, and visual acuity on whole-field scotopic sensitivity screening for glaucoma in rural Taiwan. Arch Ophthalmol 1995 113: 1138-1143.
30. **Conte M, Zemon V, Camisa J, Milkman N.** Comparing psychophysical and VEP contrast sensitivity. Invest Ophthalmol Vis Sci 1983 24: S47.
31. **Cuenca N, Kolb H.** Circuitry and role of substance P-immunoreactive neurons in the primate retina. J Comp Neurol 1998 393: 439-456.
32. **Czigler I, Balázs L, Grósz A et al.** Int J Psychophysiol 1999 33: 127.
33. **Daitch JM, Green DG.** Contrast sensitivity of the human peripheral retina. Vision Res 1969 9: 947-952
34. **Davis HQ, Kamimori GH, Kulesh DA et al.** Visual performance with the Aviator Night Vision Imaging System (ANVIS) at a simulated altitude of 4300 meters. Aviat Space Environ Med 1995 66: 430-434.
35. **Davis S, Tress B, King J.** Primary empty sella syndrome and benign intracranial hypertension. Clin Exp Neurol 1978 15: 248-257.
36. **de Vries Knoppert WA.** Primary empty sella syndrome and benign intracranial hypertension. Doc Ophthalmol 1986 61: 319-325.
37. **Demb JB, Boynton GM, Best M, Heeger DJ.** Psychophysical evidence for a magnocellular pathway deficit in dyslexia. Vision Res 1998 38: 1555-1559.
38. **Derefeldt G, Lennerstand G, Lundt B.** Age variations in normal human contrast sensitivity. Acta Ophthalmol 1979 57: 679-690.
39. **Derrington AM, Lennie P** Spatial and temporal contrast sensitivities of neurones in lateral geniculate nucleus of macaque. J Physiol (London) 1984 357:219-240.
40. **Diener HC.** How can PET scans help us understand headache mechanisms. Cephalalgia 1999 23: 15-18.
41. **Digre KB.** Not so benign intracranial hypertension. Br Med J 2003 326: 613-614.
42. **Drum B, Armaly MF, Huppert W.** Scotopic sensitivity loss in glaucoma. Arch Ophthalmol 1986 104: 712-717.
43. **Enroth-Cugell C, Hertz BG, Lennie P.** Convergence of rod and cone signals in the cat's retina. J Physiol (London) 1977 269: 297-318.
44. **Enroth-Cugell C. Robson J.G.** J Physiol (London) 1966 187: 517-552.
45. **Fiorentini A, Burr DC, Morrone CM.** Temporal characteristics of colour vision: VEP and psychophysical measurements. In Valberg A, Lee BB. (eds.) From Pigments to Perception NATO ASI Series, New York: Plenum. 1991 pp. 139-149.

46. **Flower B, Nathoo A.** Slowing due to acute hypoxia originates early in the visual system. Aviat Space Environ Med 1997 68: 886-889.
47. **Foley KM, Posner JB.** Does pseudotumor cerebri cause the empty sella syndrome? Neurology 1975 25: 565-569.
48. **Frederick JM, Rayborn ME, Laties AM, Lam DM, Hollyfield JG.** Dopaminergic neurons in the human retina. J Comp Neurol 1982 210: 65-79.
49. **Fusco R, Magli A, Guacci P, Tenore A.** Empty sella syndrome. A case report. Ophthalmologica 1988 196: 92-97.
50. **Ginsburg AP, Evans DW, Cannon MW, Owsley C, Mulvanny D.** Large-sample norms for contrast sensitivity. Optom Physiol 1984 61: 80-84.
51. **Glovinsky Y, Quigley HA, Drum B, Bissett RA, Jampel HD.** A whole-field scotopic retinal sensitivity test for the detection of early glaucoma damage. Arch Opthalmol 1992 110: 486-490.
52. **Gouras P, Link K.** Rod and cone interaction in dark-adapted monkey ganglion cells. J Physiol (London) 966 184: 499-510.
53. **Granit R.** Centrifugal and antidromic effects on ganglion cells of retina. J Neurophysiol 1955 18: 388-411
54. **Grünert U.** Anatomical evidence for rod input to the parvocellular pathway in the visual system of the primate. Eur J Neurosci 1997 9: 617-621.
55. **Guinto G, del Valle R, Nishimura E, Mercado M, Nettel B, Salazar F.** Primary empty sella syndrome: the role of visual system herniation. Surg Neurol 2002 58: 42-47.
56. **Gutowski NJ, Heron JR, Scase MO.** Early impairment of foveal magno- and parvocellular pathways in juxta chiasmal tumours Vision Res 1997 37: 1401-1408.
57. **Harris A, Arend O, Danis RP et al.** Hyperoxia improves contrast sensitivity in early diabetic retinopathy. Br J Ophthalmol 1996 80: 209-213.
58. **Hassler R.** Comparative anatomy of the central visual systems in day- and night-active primates. In Hassler R, Stephan H. (Eds.), Evolution of the Forebrain, Stuttgart: Verlag. 1966
59. **Hawken MJ, Parker AJ.** Contrast sensitivity and orientation sensitivity in lamina IV of the striate cortex of old world monkey. Exp Brain Res 1984 54: 367-372.
60. **Headache Classification Committee of the International Headache Society.** Classification and diagnostic criteria for headache disorders, cranial neuralgia, and facial pain. Cephalalgia 1988 8 Suppl 7: 1-96

61. **Hicks TP, Lee BB, Vidyasagar TR.** The responses of cells in macaque lateral geniculate nucleus to sinusoidal gratings. J Physiol (London) 1983 337: 183-200.

62. **Hoffmann KP, Stone J.** Retinal input to the nucleus of the optic tract of the cat assessed by antidromic activation of ganglion cells Exp Brain Res 1985 59: 395-403.

63. **Hofmann MI, Barnes CS, Hallett PE.** Detection of briefly flashed sine-gratings in dark-adapted vision. Vision Res 1990 30: 1453-1466.

64. **Janaky M, Benedek G.** Visual evoked potentials during the early phase of optic nerve compression in the orbital cavity. Doc Ophthalmol 1992 81: 197-208.

65. **Jordan RM, Kendall JW, Kerber CW.** The primary empty sella syndrome: analysis of the clinical characteristics, radiographic features, pituitary function and cerebrospinal fluid adenohypophysial hormone concentrations. Am J Med 1977 62: 569-580.

66. **Kaplan E, Shapley RM.** The primate retina contains two types of ganglion cells, with high and low contrast sensitivity. Proc Natl Acad Sci USA 1986 83: 2755-2757.

67. **Kelly DH.** Adaptation effects on spatio-temporal sine-wave thresholds. Vision Res 1972 12: 89-101.

68. **Kéri S, Antal A, Kálmán J et al.** Early visual impairment is independent of the visuocognitive and memory disturbances in Alzheimer's disease. Vision Res 1999 39: 2261-2265.

69. **Keri S, Antal A, Szekeres G, Benedek G, Janka Z.** Visual information processing in patients with schizophrenia: evidence for the impairment of central mechanisms. Neurosci Lett 2000 293: 69-71.

70. **Kéri S, Szekeres G, Antal A. et al.** Spatiotemporal visual processing in schizophrenia. J Neuropsychiatry Clin Neurosci 2002 14: 190-196.

71. **Khalil NM.** Investigations of visual function in migraine using visual evoked potentials and visual psychophysical tests. PhD Thesis. University of London 1991.

72. **Kiyama H, Katayama Y, Hillyard CJ, Girgis S, MacIntyre I, Emson PC, Tohyama M.** Occurrence of calcitonin gene-related peptide in the chicken amacrine cells. Brain Res 1985 327: 367-369.

73. **Klistorner AI, Graham SL.** Early magnocellular loss in glaucoma demonstrated using the pseudorandomly stimulated flash visual evoked potential. J Glaucoma 1999 8: 140-148.

74. **Klistorner A, Crewther DP, Crewther SG.** Separate magnocellular and parvocellular contributions from temporal analysis of the multifocal VEP. Vision Res 1997 37: 2161-2169.

75. **Kobrick JL, Crohn E, Shukitt B et al.** Operation Everest II: lack of an effect of extreme altitude on visual contrast sensitivity. Aviat Space Environ Med 1988 59: 160-164.

76. **Kobrick JL.** Effects of hypoxia on the luminance threshold for target detection. Aviat Space Environ Med 1983 54: 112-115.

77. **Koenderink JJ, Bouman MA, Bueno de Mesquita AE, Slappendel S.** Perimetry of contrast detection thresholds of moving spatial sine wave patterns IV. The influence of the mean retinal illuminance. J Optical Soc Am 1978 68: 860-865.

78. **Kremers J, Lee BB, Kaiser PK.** Sensitivity of macaque retinal ganglion cell and human observers to combined luminance and chromatic temporal modulation. J Optical Soc Am 1992 9: 1478-1485.

79. **Kremers J, Lee BB, Pokorny J, Smith VC.** Responses of macaque ganglion cells and human observers to compound periodic waveforms. Vision Res 1993 33(14): 1997-2011

80. **Kubova Z, Kuba M, Spekreijse H, Blakemore C.** Contrast dependence of motion-onset and pattern-reversal evoked potentials. Vision Res 1995 35: 197-205.

81. **Kulikowski JJ.** Some stimulus parameters affecting spatial and temporal resolution of human vision. Vision Res 1971 1: 83-93.

82. **Kulikowski JJ.** On the nature of visual evoked potentials, unit responses and psychophysics. In **alberg A, Lee BB.** (Eds.) From Pigments to Perception, NATO ASI Series, New York: Plenum. 1991 pp. 197-209.

83. **Langerhorst CT, Safran AB.** Progressive shrinkage of the visual field during automated perimetry following traumatic brain injury. Patients' experience. Neuro-Ophthalmology 1998 20: 177-185.

84. **Lawden MC, Eke T, Degg C, Harding GF, Wild JM.** Visual field defects associated with vigabatrin therapy. J Neurol Neurosurg Psychiatry 1999 67: 716-722.

85. **Leao, A.A.P.** Spreading depression of activity in the cerebral cortex. J Neurophysiol 1944 7: 359-390.

86. **Lee BB, Smith VC, Pokorny J, Kremers J.** Rod inputs to macaque ganglion cells. Vision Res 1997 37: 2813-2828.

87. **Lee BB, Martin PR, Valberg A, Kremers J.** Physiological mechanisms underlying psychophysical sensitivity to combined luminance and chromatic modulation. J Optical Soc Am 1993 10: 1403-1412.

88. **Lennie P.** Parallel visual pathways: a review. Vision Res 1980 20: 561-594.

89. **Lennie P, Fairchild MD**. Ganglion cell pathways for rod vision. Vision Res 1994 34: 477-482.

90. **Linsenmeier RA**. Electrophysiological consequences of retinal hypoxia. Graefes Arch Clin Exp Ophthalmol 1990 228: 143-150.

91. **Long GM, May PA**. Dynamic visual acuity and contrast sensitivity for static and flickered gratings in a college sample. Optometry and Visual Sci 1992 69: 915-922.

92. **Lundt BL, Lennerstand G, Derefeldt G.** Central and peripheral normal contrast sensitivity for static and dynamic gratings. Acta Ophtahlmol 1983 61: 171-182.

93. **Mascia A**. Dopamine and migraine: a review of pharmacological, biochemical, neurophysiological, and therapeutic data. Cephalalgia 1998 18: 174-182.

94. **McClure RK**. The visual backward masking deficit in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2001 25: 301-311.

95. **McFadzean RM.** The empty sella syndrome. A review of 14 cases. Trans Ophthalmol Soc UK 1983 103: 537-542.

96. **McKendrick AM, Johnson CA, Anderson AJ, Fortune B.** Elevated vernier acuity thresholds in glaucoma. Invest Ophthalmol Vis Sci 2002 43: 1393-1399.

97. **Merigan WH, Maunsell JH.** How parallel are the primate visual pathways? Annu Rev Neurosci 1993 16: 369-402.

98. **Miki A, Nakajima T, Hasebe H, Abe H.** Functional magnetic resonance imaging of visual function in postpapilledema optic atrophy. J Neuroophthalmol 1997 17: 223-225.

99. **Morgan IG, Wellard JW, Boelen MK**. A role for the enkephalin-immunoreactive amacrine cells of the chicken retina in adaptation to light and dark. Neurosci Lett 1994 174: 64-66.

100. **Nakayama K, Mackeben M**. Steady state visual evoked potentials in the alert primate.Vision Res 1982 22: 1261-1271.

101. **Nelson TO, Dunlosky J, White DM et al**. Cognition and metacognition at extreme altitudes on Mount Everest. J Exp Psychol Gen 1990 119: 367-374.

102. **Oelkers R, Grosser K, Lang E, Geisslinger G, Kobal G, Brune K, Lotsch J**. Visual evoked potentials in migraine patients: alterations depend on pattern spatial frequency. Brain 1999 122: 1147-1155.

103. **Pammer K, Wheatley C**. Isolating the M(y)-cell response in dyslexia using the spatial frequency doubling illusion. Vision Res 2001 41: 2139-2147.

104. **Patel AS.** Spatial resolution by the human visual system. The effect of mean retinal illuminance. J Optical Soc Am 1966 56: 689-694.

105. **Polyak SL** The Retina. University of Chicago Press, Chicago. 1941

106. **Pourcho RG**. Dopaminergic amacrine cells in the cat retina. Brain Res 1982 252: 101-109.

107. **Purpura K, Kaplan E, Shapley RM**. Background light and the contrast gain of primate P and M retinal ganglion cells. Proc Natl Acad Sci USA 1988 85: 4534-4537.

108. **Reese BE, Cowey** A. The neurological consequences of a sub-chiasmal tumor on the retino-geniculo-striate pathway of a macaque monkey. Clin Vision Sci 1989 4: 341-356.

109. **Regan D, Maxner C.** Orientation-selective visual loss in patients with Parkinson's disease. Brain 1987 110: 415-432.

110. **Regan D, Lee BB**. A comparison of the 40 Hz response in man and the properties of macaque ganglion cells. Visual Neurosci 1993 10: 439-445.

111. **Regan D**. Evoked potentials specific to spatial patterns of luminance and colour. Vision Res 1973 13: 2381-2402.

112. **Regan D.** Human Brain Electrophysiology. New York, Elsevier. 1989

113. **Regard M, Landis T, Casey J et al**. Cognitive changes at high altitude in healthy climbers and in climbers developing acute mountain sickness. Aviat Space Environ Med 1991 62: 291-295.

114. **Robson JG.** Spatial and temporal contrast sensitivity of the visual system. J Optical Soc Am 1966 56: 1141-1142.

115. **Sage MR, Chan ES, Reilly PL.** The clinical and radiological features of the empty sella syndrome. Clin Radiol 1980 31: 513-519.

116. **Schiller PH.** Single unit analysis of backward visual masking and metacontrast in the cat lateral geniculate nucleus. Vision Res 1968 8: 855-866.

117. **Schefrin BE, Tregear SJ, Harvey LO Jr, Werner JS**. Senescent changes in scotopic contrast sensitivity. Vision Res 1999 39: 3728-3723.

118. **Schlaepfer TE, Bartsch P, Fisch HU**. Paradoxical effects of mild hypoxia and moderate altitude on human visual perception. Clin Sci 1992 83: 633-636.

119. **Schmeisser ET, Gagliano DL, Santiago-Marini J.** Visual system effects of exercise on Mauna Kea at 2,200 and 4,200 meters altitude. Mil Med 1997 162: 186-189.

120. **Schneider GE**. Two visual systems. Science 1969 163: 895-902.

121. **Schoenen J.** Cortical electrophysiology in migraine and possible pathogenetic implications. Clin Neurosci 1998 5: 10-17.

122. **Schultze M**. Zur Anatomie und Physiologie der Retina. Arch Mikr Anat 1866 2: 165-175.

123. **Schwartz BD, Maron BA, Evans WJ, Winstead DK.** High velocity transient visual processing deficits diminish ability of patients with schizophrenia to recognize objects. Neuropsychiatry Neuropsychol Behav Neurol 1999 12: 170-177.

124. **Shabana N, Peres VC, Carkeet A, Chew PT.** Motion perception in glaucoma patients: a review. Surv Ophthalmol 2003 48: 92-106.

125. **Shan Y, Moster ML, Roemer RA, Siegfried JB.** Abnormal function of the parvocellular visual system in anisometropic amblyopia. J Pediatr Ophthalmol Strabismus 2000 37: 73-78.

126. **Shapley R.** Parallel pathways in the mammalian visual system. Ann N Y Acad Sci 1982 388: 11-20.

127. **Shapley R.** Visual sensitivity and parallel retinocortical channels. Annu Review Psychol 1990 41: 635-658.

128. **Shibata K, Osawa M, Iwata M.** Pattern reversal visual evoked potentials in classic and common migraine. J Neurol Sci 1997 145: 177-181.

129. **Sicuteri F. Nicolodi M. DelBianco PL. Del Bene E.** Decentralization monoamine super-sensitivity of migraine and opiate abstinence: Common features and different target mechanisms? Int J Clin Pharm Res 1997 17: 67-73.

130. **Skottun BC.** The magnocellular deficit theory of dyslexia: the evidence from contrast sensitivity. Vision Res 2000 40: 111-127.

131. **Sletteberg O, Bertelsen T, Hovding G.** The prognosis of patients with hysterical visual impairment. Acta Ophthalmol 1989 67: 159-163.

132. **Spaziante R, de Divitiis E, Stella L, Cappabianca P, Genovese L.** The empty sella. Surg Neurol 1981 16: 418-426.

133. **Steinman SB, Steinman BA, Garzia RP.** Vision and attention. II: Is visual attention a mechanism through which a deficient magnocellular pathway might cause reading disability? Optom Vision Sci 1998 75: 674-681.

134. **Stivalet P, Leifflen D, Poquin D et al.** Positive expiratory pressure as a method for preventing the impairment of attentional processes by hypoxia. Ergonomics 2000 43: 474-485.

135. **Stone J, Maslim J, Valter-Kocsi K et al.** Mechanisms of photoreceptor death and survival in mammalian retina. Prog Retin Eye Res 1999 18: 689-735.

136. **Tagliati M, Sabbadini M, Bernardi B, Silvestrini M.** Multichannel visual evoked potentials in migraine. Electroencephalogr Clin Neurophysiol 1995 96: 1-5.

137. **Takanashi J, Suzuki H, Nagasawa K, Kobayashi K, Saeki N, Kohno Y.** Empty sella in children as a key for diagnosis. Brain Dev 2001 23: 422-423.

138. **Tassinari G, Marzi CA, Lee BB, Di Lollo V, Campara D.** A possible selective impairment of magnocellular function in compression of the anterior visual pathways. Brain Res 1999 127: 391-401.

139. **Thompson DA, Drasdo N.** Colour, contrast and the visual evoked potential. Ophthalmic Physiol Opt 1992 12: 225-228.

140. **Tobimatsu S, Tomoda H, Kato M.** Parvocellular and magnocellular contributions to visual evoked potentials in humans: stimulation with chromatic and achromatic gratings and apparent motion. J Neurol Sci 1995 134: 73-82.

141. **Trevarthen C.B.** Two mechanisms of vision in primates Psychol Forsch 1968 31:299-337.

142. **Tweel LH, van der Spekreijse H.** Psychophysics and electro-physiology of a rod-achromat. Doc. Ophthalmol. Proc Ser Xth ISCERG Symposium, Los Angeles 1972 Dr. W. Junk BV. Publishers, The Hague, 1973

143. **Ungerleider L.G., Mishkin M.** Two cortical visual systems. In: Analysis of Visual Behavior, eds. Ingle D.J., Goodale M.A., Mansfield R. J.W., Cambridge, MA, MIT Press. 1982 pp. 549-596.

144. **Valberg A, Rudvin I.** Possible contributions of magnocellular- and parvocellular pathway cells to transient VEPs. Visual Neurosci 1997 14: 1-11.

145. **van der Kamp W, Maassen VanDenBrink A, Ferrari MD, van Dijk JG.** Interictal cortical hyperexcitability in migraine patients demonstrated with transcranial magnetic stimulation. J Neurol Sci 1996 139: 106-110.

146. **Van Meeteren A, Vos JJ.** Resolution and contrast sensitivity at low luminances. Vision Research 1972 12: 825-833.

147. **Vidyasagar TR, Pammer K.** Impaired visual search in dyslexia relates to the role of the magnocellular pathway in attention. Neuroreport 1999 10: 1283-1287.

148. **Vleugels L, Lafosse C, van Nunen A, Charlier M, Ketelaer P, Vandenbussche E.**Visuoperceptual impairment in MS patients: nature and possible neural origins. Mult Scler 2001 7: 389-401.

149. **Vogt U, Morland A, Migdal C, Ruddock K.** Spatial and temporal visual filtering in patients with glaucoma and ocular hypertension. Eye 1998 12: 691-696.

150. **Weisberg LA.** Computed tomography in benign intracranial hypertension. Neurology 1985 35: 1075-1078.

151. **Wolf JE, Arden GB.** Selective magnocellular damage in melanoma-associated retinopathy: comparison with congenital stationary nightblindness. Vision Res 1996 36: 2369-2379.